BRAINSTEM AUDITORY EVOKED RESPONSES IN NEWLY DIAGNOSED HYPOTHYROID INDIVIDUALS

Dissertation submitted to

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY,

CHENNAI – 600032

In partial fulfillment of the requirement for the degree of

Doctor of Medicine in Physiology (Branch V)

M.D. (PHYSIOLOGY)

APRIL 2015

DEPARTMENT OF PHYSIOLOGY

COIMBATORE MEDICAL COLLEGE

COIMBATORE – 14

CERTIFICATE

This dissertation entitled **"BRAINSTEM AUDITORY EVOKED RESPONSES IN NEWLY DIAGNOSED HYPOTHYROID INDIVIDUALS"** is submitted to The Tamil Nadu Dr. M.G. R Medical University, Chennai, in partial fulfillment of regulations for the award of M.D. Degree in Physiology in the examinations to be held during April 2015.

This dissertation is a record of fresh work done by the candidate **Dr. V. ROSELINE JESINTHA ,** during the course of the study (2012-2015).

This work was carried out by the candidate herself under my supervision.

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DECLARATION

I Dr.V.Roseline Jesintha solemnly declare that the dissertation entitled **"BRAINSTEM AUDITORY EVOKED RESPONSES IN NEWLY DIAGNOSED HYPOTHYROID INDIVIDUALS"** was done by me at Coimbatore Medical College, during the period from August 2013 to June 2014. Under the guidance and supervision of **Dr. L.Manonmani. M.D.,** Associate Professor, Department of Physiology, Coimbatore Medical College, Coimbatore. This dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of the requirement for the award of M.D. Degree (Branch - V) in Physiology.

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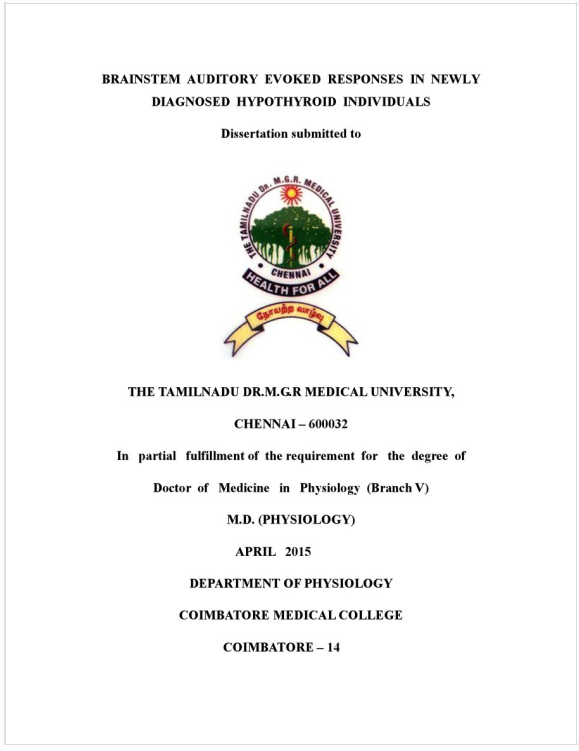

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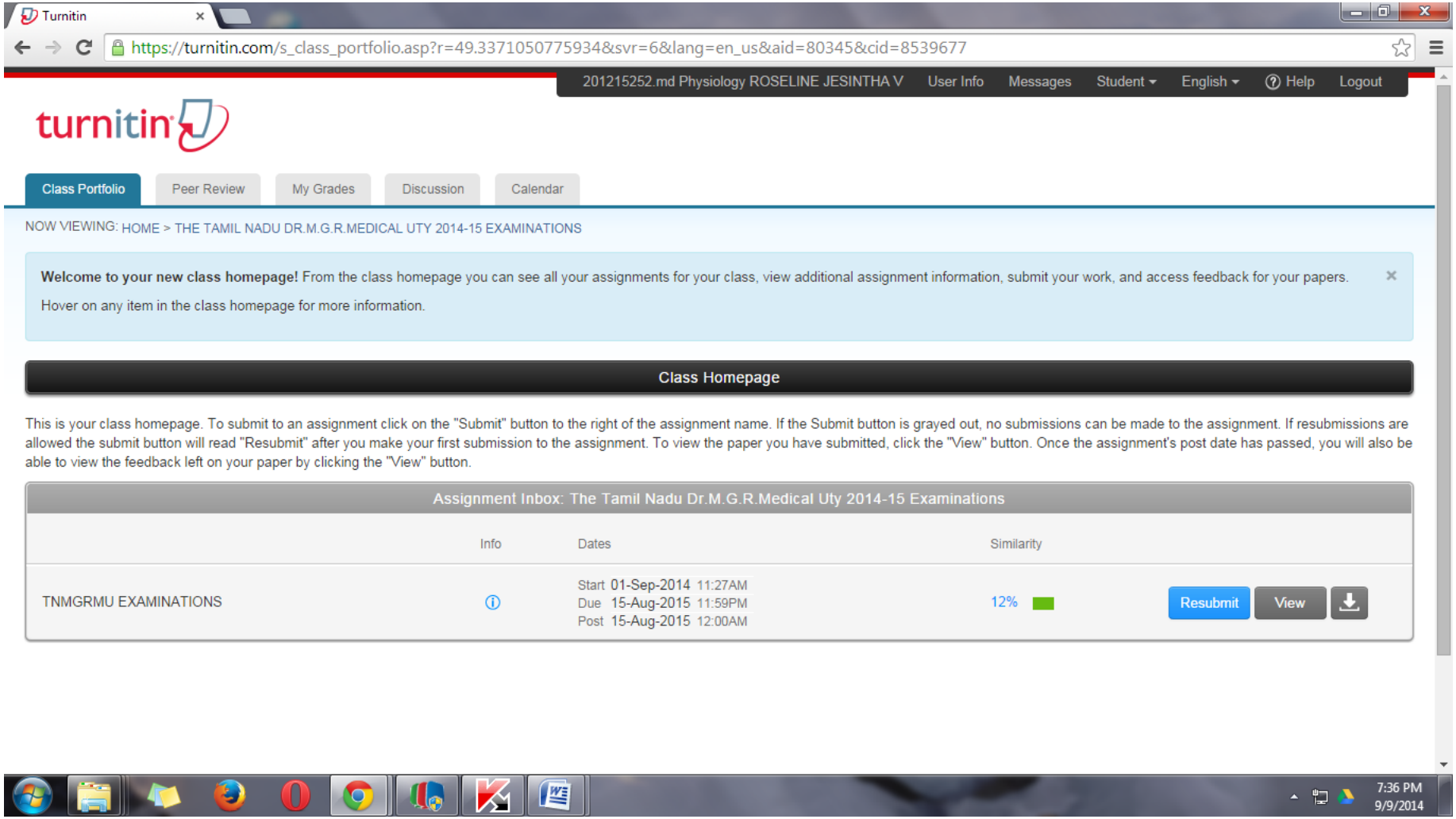
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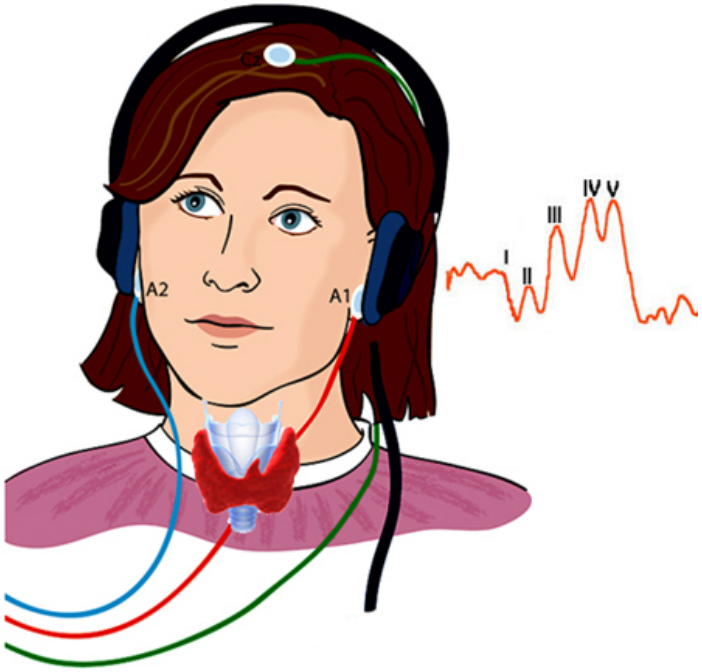


ABBREVIATIONS USED IN THE STUDY

BAER	Brainstem Auditory Evoked Response
TG	Thyroglobulin
DIT	Diiodotyrosine
MIT	Monoiodotyrosine
TSH	Thyroid Stimulating Hormone
NCoR	Nuclear receptor Co repressor
SMRT	Silencing Mediator for Retinoic Acid and Thyroid Hormone Receptor
SCH	Sub Clinical Hypothyroidism
EEG	Electro Encephalogram
IPL	Inter Peak Latency
DCN	Dorsal Cochlear Nucleus
AVCN	Antero Ventral Cochlear Nucleus
PVCN	Postero Ventral Cochlear Nucleus
CHL	Conductive Hearing Loss
SNHL	Sensori Neural Hearing Loss
ELISA	Enzyme Linked Immuno Sorbent Assay
BMI	Body Mass Index

BRAINSTEM AUDITORY EVOKED RESPONSES IN NEWLY DIAGNOSED HYPOTHYROID INDIVIDUALS

Abstract

Background: Hypothyroidism is one of the most common endocrine disorder, affecting the females predominantly than males. Thyroid hormone deficiency affects almost all organ system of our body including auditory pathway. Sensori neural hearing loss is the most common otolaryngological manifestations of thyroid dysfunction. Evoked potentials are the best methods which have been used extensively in the study of brain disturbances and to a lesser degree in metabolic diseases. Brainstem Auditory Evoked Response (BAER) is one of the method used for assessing the pathology in the brainstem auditory pathway.

Aim and Objectives: To evaluate the auditory sensory process in the brainstem by using Brainstem auditory evoked responses in the newly diagnosed hypothyroid individuals.

Study Design : This is a Cross sectional study

Participants : Forty newly diagnosed hypothyroid females of 20 – 50 years were taken as cases and forty age matched females were considered as controls. The hypothyroidism was diagnosed by estimating the serum levels of free T_3(fT_3), free T_4 (fT_4) and TSH.

Methodology : After getting informed written consent, a thorough clinical assessment by detailed history ,systemic and neuro - otological examination have been done in both cases and controls. The absolute latencies and interpeak latencies of BAER were recorded using Neuroperfect EMG 2000 system with installed BAER in the research laboratory, Department of Physiology, Coimbatore Medical College, Coimbatore and the data were analyzed by student unpaired t test.

Results : The absolute latencies I, III, V and inter peak latencies I- III, III-V, I – V were significantly prolonged in newly diagnosed hypothyroid females ($p < 0.0001$) and also there was direct correlation between thyroid profile changes and the BAER latencies.

Conclusion : The results of the present study suggests that hypothyroidism affects the auditory pathway in diffuse pattern and the involvement of auditory pathway in thyroid hormone deficiency can be identified by using BAER at an early stage itself. The prolongation of BAER latencies in newly diagnosed hypothyroid females was due to defective myelination of neural pathways and diminished cerebral metabolism. Hence it may be worthwhile to add the BAER recordings in the list of screening tools for a more accurate and early assessment of neurological involvement in hypothyroid individuals .

Keywords : Hypothyroidism, Brainstem Auditory Evoked Responses, Sensorineural hearing loss.

INTRODUCTION

Hypothyroidism is the most common prevailing endocrine disorder among all endocrine maladies. It is an altered metabolic state, when the body produces insufficient amount of thyroid hormone. Hypothyroidism is not only a disorder of endocrine system, it also affects almost all the organ system of our body. The wide range of disease severity from asymptomatic state to coma makes it an elusive clinical entity. [1]

Hypothyroidism is referred to as "Silent Disease" because the early stage of disease is asymptomatic. About 1.6 billion people are at risk of getting thyroid disorders worldwide. [2] According to National Health and Nutrition Examination Survey III (NHANES) approximately 4- 5% of population in the developed world is suffering from hypothyroidism and about 4 -15% of people by subclinical hypothyroidism. [3]

The most common cause of hypothyroidism is iodine deficiency. In India, hypothyroidism is classified under the group of Iodine Deficient Disorders (IDD). [4] Since 1983 India has been following the Universal Salt Iodization Programme. As a result of it, there has been a decline in the prevalence of IDD. [5] In 2004, WHO assessment of global iodine status documented that India has

optimal iodine nutrition and now is undergoing transition from iodine deficiency to sufficiency phase. [6] But a nationwide comprehensive epidemiological study done in the eight cities of India found that the prevalence of hypothyroidism was 10.95%. One third of them (3.47%) are not even aware of their disease . Females are more prone to have hypothyroidism than males (15.86% to 5.02%). Unnikrishnan AG et al has observed high prevalence of hypothyroidism among the Indian adult population. [4]

Thyroid hormone governs the rate of metabolism of fats, carbohydrates, proteins and also regulates the timing and pace of the CNS development. It is extremely important for the growth of cerebral, cerebellar cortex in terms of axonal proliferation, branching of dendrites, synaptogenesis, and myelination . Thyroid hormone enhances the wakefulness, response to various stimuli like auditory sensation, learning and memory capacity. [7]

By enhancing the gene expression it influences the synthesis of myelin. Myelin synthesis is an important factor determining the speed of impulse transmission along the complex neural pathway which mediates the evoked potentials. [8] So thyroid hormone deficiency leads to delayed neuronal conduction along the central

nervous system as well as the peripheral nervous system which reduces the perception of all the sensory stimuli.

About 60% to 80% of the patients may have features of central nervous system dysfunction like delayed mentation, depression and sensory deficits.[9] Among the sensory dysfunctions hearing loss is an invisible abnormality which will lead to devastating consequences in interpersonal communication, psychosocial wellbeing, quality of life and economic independence.

About 25 to 30% of the adult hypothyroid patients are having hearing loss. In 1948 Means et al stated that hearing loss is one of the troublesome symptom of hypothyroidism and it may be conductive, sensorineural or mixed hearing loss.[10] Being a metabolic hormone, thyroid hormone deficiency leads to reduction in the cell energy production, oxygenation and metabolism of all the organs including inner ear structures like stria vascularis and the organ of corti.[11]

Thyroid hormone deficiency produces delay in the impulse transmission which leads to alterations in hearing threshold . All these neurological complications of hypothyroidism will resolve completely with thyroid hormone replacement especially when diagnosed at the early stage.[12]

Malik et al said that in hypothyroid patients the site of lesion in auditory pathway remains speculative and it may be at several levels like at middle ear, at cochlea and retro cochlear sites. [13]

Hearing loss in infants and children due to congenital hypothyroidism results in serious impairment in language, communication skills, cognitive and emotional development. In adults hearing loss will lead to loneliness, social isolation, psychiatric disturbances, depression, occupational stress and relatively low earnings. [14] There are literatures pointing out that early treatment of hypothyroidism will reverse the hearing loss. [11, 15-17]

The integrity of the auditory pathway is essential for the capture of the acoustic signal by the external ear to the coding of signals in the auditory cortex. Impedance audiometry, Tonal threshold audiometry and electrophysiological studies can be used to assess the auditory pathway in hypothyroid patients. Among the electrophysiological studies evoked potentials provide a more reliable and objective measure of the integrity of the related sensory pathway.[18]

Brainstem Auditory Evoked Response (BAER) has emerged as an effective method of revealing the involvement of auditory pathway even in asymptomatic stage itself. [9] Brainstem Evoked

Auditory Response are produced in response to brief auditory stimulation. [19,20] In this technique following a brief acoustic stimulus, a series of potentials are generated which corresponds to the sequential activation of peripheral, pontomedullary, pontine and midbrain portion of auditory pathway. So BAER helps to evaluate the integrity of the auditory pathway.[20] Persons who are having abnormal brainstem response to auditory stimuli more prone to develop Sensory neural Hearing loss(SNHL). [21]

Howarth and Lloyd proposed that perceptive deafness is the most common type of hearing loss in hypothyroidism. [10] Von't Hoff and Stuart,[22] Parving et al [23] and Isam Al[24] also had found that sensory neural hearing loss was the predominant type in hypothyroid patients.

Now a days BAER is mainly used for screening the preterm infants and also prior to cochlear implantation. The BAER recording for finding the functional integrity of auditory pathway is rarely performed in hypothyroid patients in neurology and otolaryngology practice. The findings of various studies stated that the delay in the auditory processing time may provide the information about the subclinical involvement of central as well as peripheral neuropathy in hypothyroid individuals. So BAER can be used as a screening

test to find the central nervous system involvement and the hearing loss in hypothyroid patients even in the earlier stage itself.

Keeping all these in mind, in this study an endeavor has been made to find the changes in the BAER in newly diagnosed hypothyroid individuals.

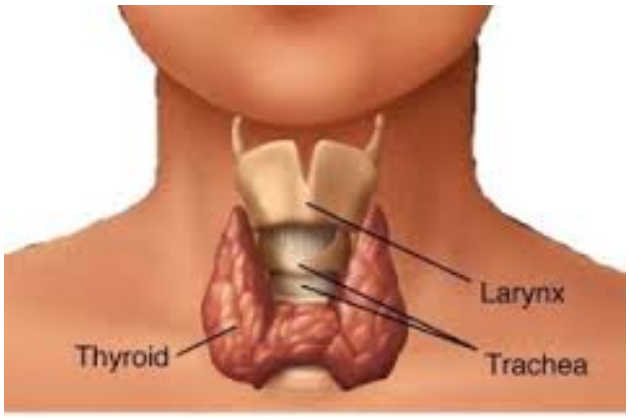
AIMS & OBJECTIVES

AIMS AND OBJECTIVES

- To record the Brainstem Auditory Evoked Responses (BAER) in newly diagnosed Hypothyroid females and Controls.
- To compare the Brainstem Auditory Evoked Responses among newly diagnosed Hypothyroid females and Controls.
- To find the correlation between thyroid profile and the BAER latencies and inter peak latencies.

REVIEW OF LITERATURE

THYROID GLAND



THOMAS WARTON

REVIEW OF LITERATURE

Thyroid gland is the first endocrine gland to be developed in the fetus. Among various hormones , from the fetal life up to the old age, thyroid hormone is the key hormone for the development and regulation of nervous system.[7] It is synthesized from the largest endocrine gland, the thyroid gland and large quantities of hormone are stored within the gland itself. It is secreted as less active pro hormone and is then converted into active form in the peripheral tissues.[25] Hypothyroidism is the most common endocrine disorder worldwide. It is associated with delayed mental processing and prolonged latencies of evoked potentials. Brainstem auditory evoked responses is a simple noninvasive procedure helps to detect the impairment of CNS as well as the auditory pathway.

History of Thyroid Gland:

Galen (130 – 210 AD) was the first person described about the thyroid gland.[26] The name "Thyroid" was given by Thomas Wharton in 1656, because of its close proximity to the thyroid cartilage. In Greek 'thyreos' means shield. In 1952 Gross and Pitt - Rivers discovered triiodothyronine ($T_{3)}$.[27]

Embryology :

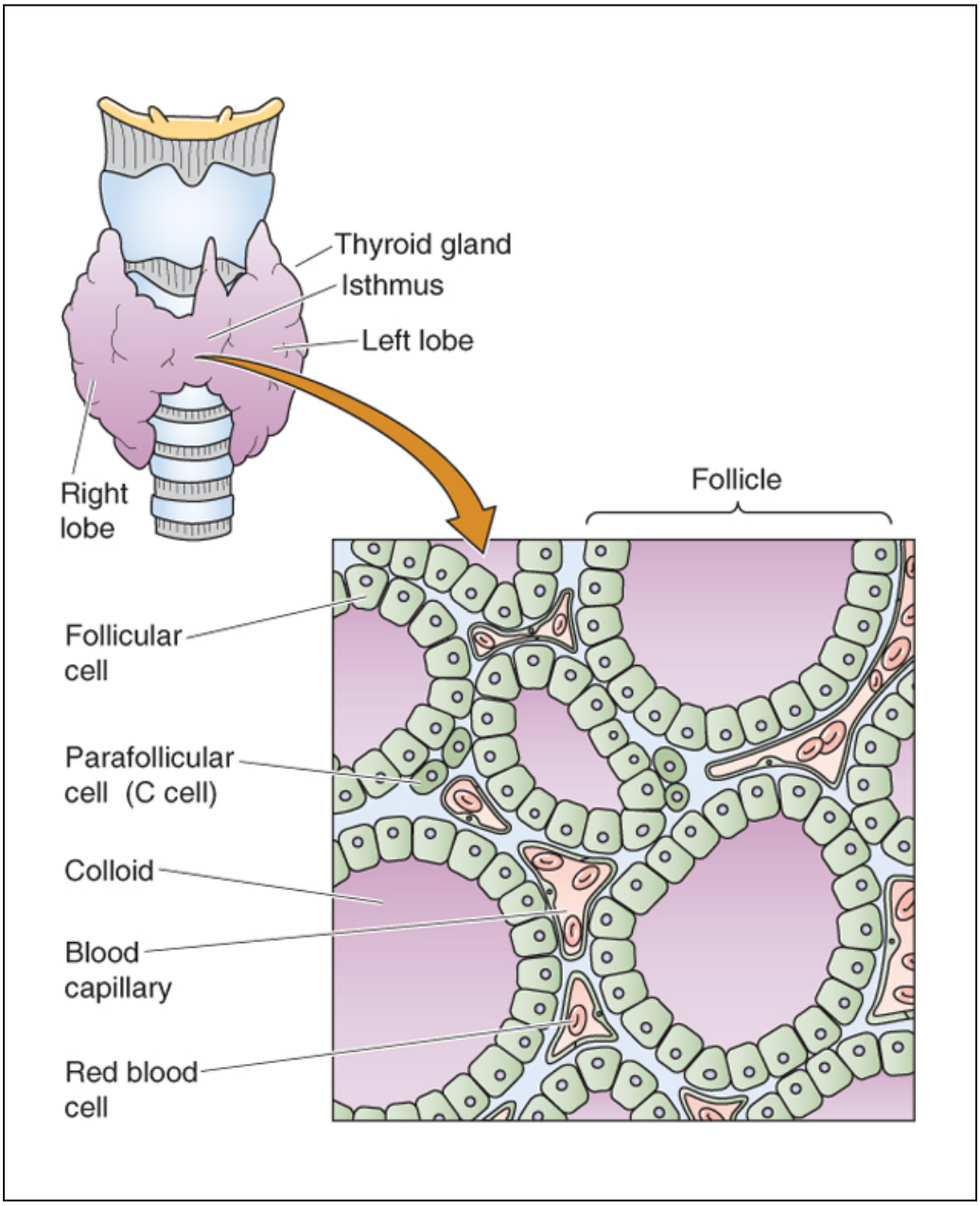
The morphogenesis of the thyroid gland begins with the formation of ***thyroid analgae*** , the primitive pharynx formed by the thickening of the endodermal epithelium of the foregut at 16th embryonic day.[28] This median thickening invaginates behind the tuberculum impar and form an outpouching of the endoderm called ***thyroglossal duct***. Thyroid gland develops from this duct and it descends caudally infront of the hyoid bone and the laryngeal cartilage, assumes bilobate shape then fuses with the fourth pharyngeal pouch at 7th week of gestation.[29] The bilobate mass divided into small median isthmus and two large lateral lobes.

Histological alterations occur within the lateral lobes and then converted into primary thyroid follicles. Subsequent buddings and differentiation produce secondary or definitive follicular cells. By the 3rd month of gestation, the follicles begin to be filled with colloid. [30]

Anatomy of Thyroid Gland:

The human thyroid gland is butterfly or capital "H" shaped that straddles the larynx and trachea at the level of 5th, 6th ,7th cervical and first thoracic vertebrae. It is yellowish brown in colour and weighs about 25g. It has two lobes which are connected by a

ANATOMY AND HISTOLOGY OF THYROID GLAND



narrow isthmus which lies in front of the trachea.[31] The lobes are roughly pyramidal in shape about 5cm long and 3 cm wide. The isthmus is quadrilateral in shape and it is 12 – 20 mm long , 20 mm wide. It corresponds to the first and second tracheal rings.[31]

Blood Supply :

It is a highly vascularized gland and each minute it receives blood flow of about 5 times the weight of the gland that is 4 – 6ml/g/min of blood.[28] This amount of blood is derived from the superior and inferior thyroid arteries. The venous return of the gland is by three veins on each side namely, the superior, inferior and middle thyroid vein which in turn drain into internal jugular vein.[32]

Histology :

The thyroid follicle is the structural unit of the thyroid gland. It is a spherical structure of about 200 - 300µm in diameter. It is lined with thyroid follicular epithelial cells (thyrocytes) which is either simple cuboidal or low columnar cells. The epithelium sits on the basal lamina, which is surrounded by fenestrated capillary network which provide the route for the hormones from the gland to the systemic circulation. The apical side of the epithelium faces the lumen of the follicle.[33]

The follicles contain pink staining gel like proteinaceous substance called colloid which forms the greatest mass of the gland. The colloid is predominantly composed of Thyroglobulin which is a glycoprotein secreted and iodinated by the follicular cells. Thyroglobulin(TG) is an inactive storage form of thyroid hormone.[7]

The size of the follicular cells and the colloid amount are dynamic, vary with the activity of the gland. When the gland is inactive, it contains large follicular cells, abundant colloid and flattened epithelial cells.[34] If the gland is active, the follicles are small and have tall columnar cells. They contain scanty colloid because of active reabsorption of colloid into the thyrocytes and they form "reabsorption lacunae" within the follicles.[7]

There are two types of cells are present .

1. Follicular cells
2. Para Follicular cells

Follicular cells are the principal cells responsible for the synthesis of T_4 & T_3. Para Follicular or C cells derived from the neural crest are widely dispersed amidst of the follicular epithelial cells which secrete Calcitonin.[25]

RECOMMENDED DIETARY INTAKE OF IODINE

Age Group	Daily Requirement
Children	90 – 120 µg/dl
Adult	150 µg/dl
Pregnant women	200 µg

DIETARY SOURCES OF IODINE

Biosynthesis of thyroid hormones

The raw materials for the synthesis of thyroid hormone are ,

- Iodide
- Thyroglobulin (TG)

Iodide:

About 50 µg/day of iodide is required for the normal production of thyroxine . Total plasma concentration of iodide is 0.3 µg/dl. To meet this daily dietary intake of iodide is 500µg is needed. [7]

Dietary sources :

Richest source is sea fish

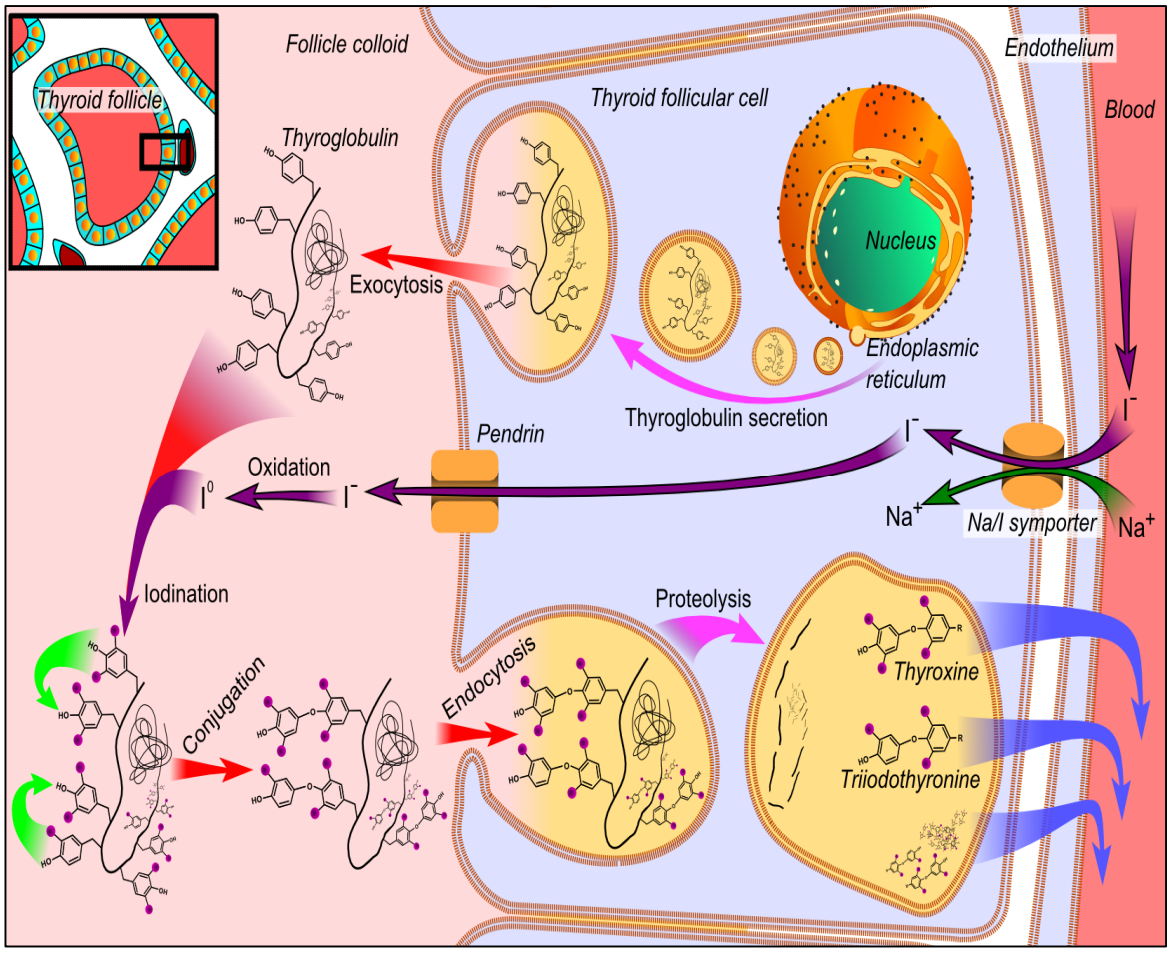
Others : bread, milk, vegetables and drinking water. [35]

One part sodium is added to every 100000 parts of sodium chloride in the common salt as prophylaxis to prevent iodine deficiency.

Thyroglobulin (TG) :

It is a large glycoprotein synthesized by the Rough endoplasmic reticulum and Golgi apparatus with Molecular weight of 660k Da. They dimerized and combine with carbohydrate moiety to form complete molecule. [34] Each molecule contains about 123 tyrosine amino acid residues. They combine with iodine and form

SYNTHESIS AND SECRETION OF THYROID HORMONE



thyroid hormone. Thus inside the thyroglobulin thyroid hormones are formed and secreted into the colloid by exocytosis which is facilitated by thyroid peroxidase enzyme. [36]

Steps in the synthesis of thyroid hormone:[28,36]

Biosynthesis of thyroid hormone is taking place in following steps:

Iodide trapping:

It is the first step in the formation of thyroid hormones. Extraction of iodide into the thyrocytes occur via Sodium Iodide Symporter (NIS or SLC5A) in the basolateral membrane.[28] The NIS cotransports one iodide ion along with two sodium ions against the electrochemical gradient. Thus iodide pump concentrates iodine 20 to 40 times as that of the plasma. If the gland is active it can concentrate as high as 250 times. [34,36]

Oxidation of iodide to iodine:

Once iodide enters into the thyroid follicular cells, it rapidly transported into the lumen by a sodium independent Chloride – Iodide counter transporter called Pendrin (SLC26A4) . Within seconds iodide is oxidized to iodine by thyroid peroxidase (TPO). Mutation of pendrin gene leads to Pendred syndrome which is characterized by thyroid dysfunction and sensorineural deafness. [34]

Organification of Thyroglobulin:

Iodination of tyrosine residues in the thyroglobulin molecule is called organification of thyroglobulin. The TG molecules are released into the lumen by exocytosis and the iodide molecules enter via Pendrin into the lumen. As soon as the oxidized iodine enters into the lumen, it binds with $1/6^{th}$ of the tyrosine residues within the TG molecule.[36]

Coupling reaction :

Iodinated tyrosine form Mono iodo tyrosine(MIT) and Diiodo tyrosine(DIT). [36] The main product of coupling reaction is thyroxin (T_4), which is formed by the condensation of two molecules of DIT in which iodine atoms are found at 3,5,3',5' positions. Whereas T_3 (triiodothyronine) is formed by the condensation of one molecule of MIT with one molecule of DIT and it contains three iodine atoms at 3,5,3' position.[36]

Storage :

Thyroid gland is the only endocrine gland that stores large amount of its hormone for many months. It is sufficient for the new hormone synthesis for about 2 - 3 months without supplementation. [36,38]

The proportion of storage is 58% of iodotyrosines (23% is MIT and 35% is DIT), 35% of T_4, 7% of T_3 and only traces amount of ReverseT_3 .[28]

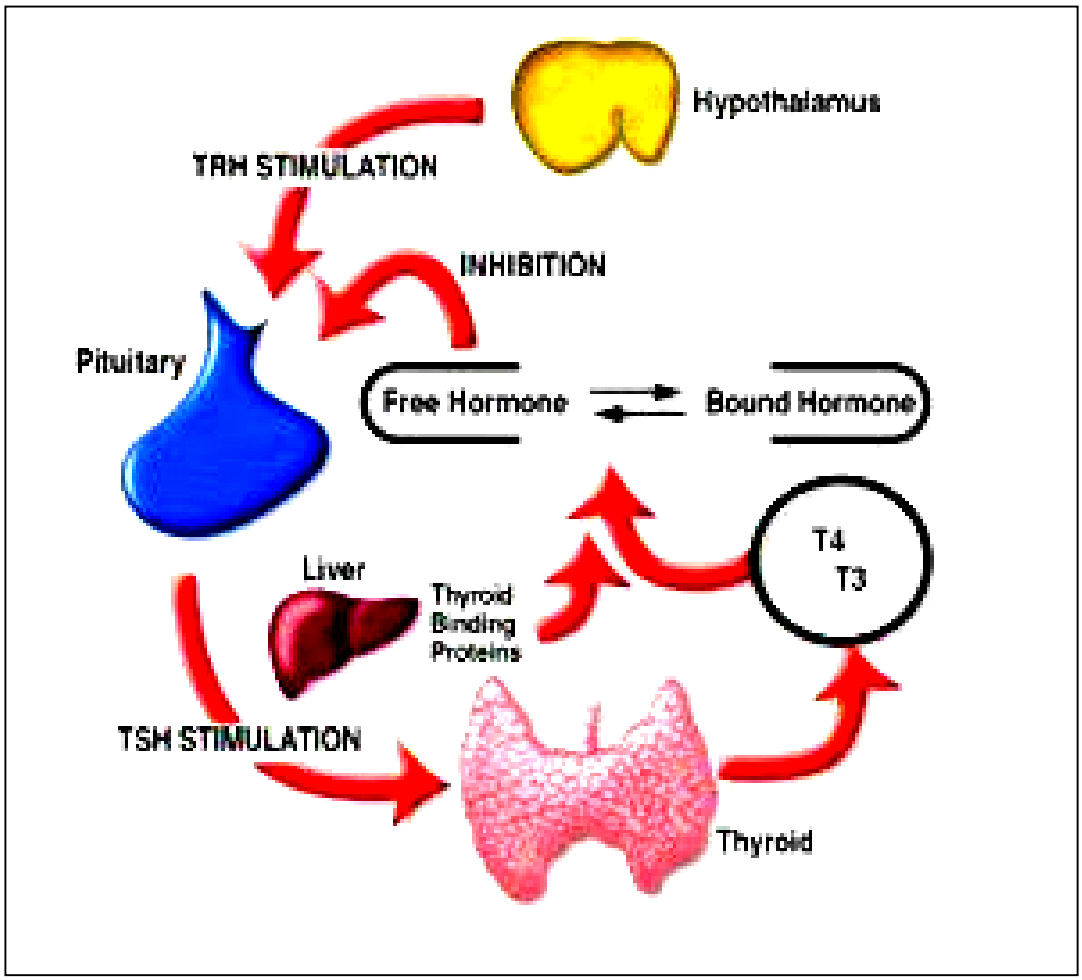
Release of thyroid hormone:

For the secretion of thyroid hormones into the circulation, the stored thyroglobulin must undergo proteolysis. It happens by binding of TG with the Megalin - a TG receptor present on the apical membrane.[7] Then endocytosis of colloid occurs with the formation of pinocytic vesicle in the apical cytoplasm. Lysosomes with the active proteases like Cathepsin D fuses with this pinocytic vesicles and releases the thyroid hormones (T_3&T_4) along with iodotyrosines (MIT&DIT). Thyroid gland releases 80µg (103nmol) of T_4, 4 µg (7nmol) of T_3 and 2 µg (3.5nmol) of RT_3 daily.[34]

Transport of thyroid hormone:

The total plasma concentration of T_4 is 8 µg/dl and T_3 is 0.15 µg/dl of which only 0.04% of T_4 and 0.4% of T_3 are in the free form.[34] The free form is the physiologically active form that acts on the target tissues.

REGULATION OF THYROID HORMONE



Majority of the hormones are in bound form and they bind with the plasma proteins like, [26]

- Thyroxin Binding Globulin (TBG)
- Albumin
- Transthyretin (TTR)

Among the three proteins TBG has high affinity for T_3 and T_4 . 70% of T_3 & T_4 bind with TBG and form large circulating reservoir for thyroid hormones. [7]

T_4 is more avidly bound to plasma proteins than T_3. It is the reason for the long half-life of T_4. Half-life of T_3 is 7 days and for T_3 is 1day. [38]

Regulation of thyroid hormone secretion:

The interplay between the thyroid hormones with Thyrotropin releasing hormone (TRH) and Thyroid stimulating hormone (TSH) helps to maintain the secretion of thyroxine. TRH secreted from the hypothalamus stimulates the anterior pituitary to secrete TSH which in turn increases the thyroid hormone secretion. The circulating free hormones send feedback signals to the hypothalamus and pituitary for regulation of the TRH, TSH release. Thus the hypothalamo pituitary thyroid axis controls the thyroid hormone secretion. [39]

Thyroid Stimulating Hormone (TSH):

It is otherwise known as Thyrotropin. It is a glycoprotein with the molecular weight of about 28kD , consists of 2 subunits α and β. The gene for the α subunit present in chromosome 6 and for the β subunit in chromosome 1. The α subunit is structurally similar to Luteinizing Hormone, Follicular Stimulating Hormone and Human chorionic Gonadotropin. The β subunit is unique and it has specific binding properties. [34,39]

TSH binds to the specific TSH receptor on the basolateral aspect of the thyroid cell. It is a G protein coupled receptor and its gene is located in the chromosome 14. It activates cyclic adenosine monophosphate (cAMP) and the phosphoinositol pathway. It leads to synthesis and secretion of thyroxine. From the iodide trapping up to the release of T_4 ,T_3 into the circulation, all steps are stimulated by TSH. It also increases the cell size and the vascularity of the gland. [7]

Auto regulation of thyroid hormone:

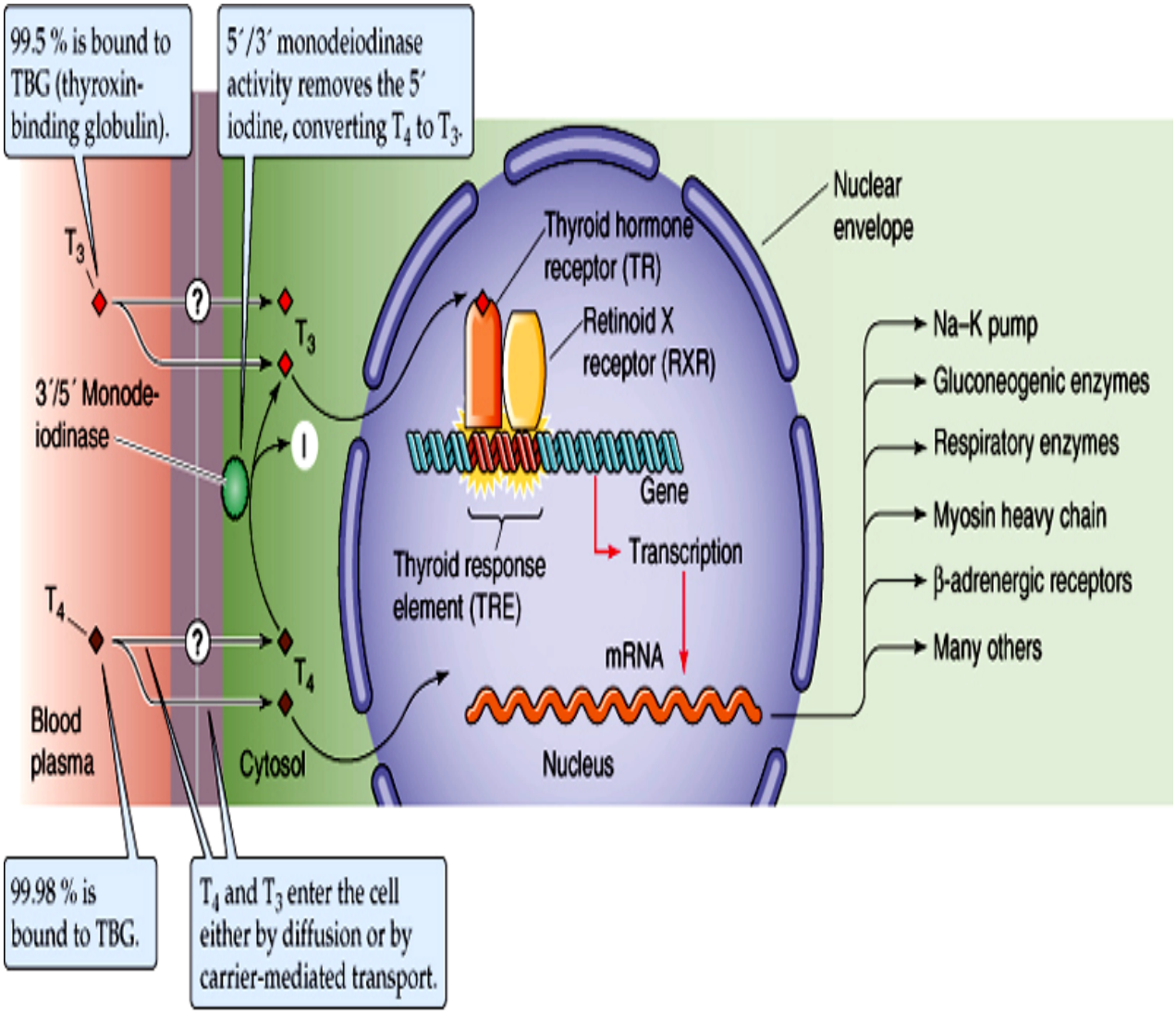
If the rate of thyroid hormone secretion increases to 1.75 times normal, eventually the TSH secretion falls to zero by the negative feedback effect of thyroxine on the anterior pituitary and the hypothalamus. T_3 causes repression of TSH β subunit expression

and decreases the TSH secretion. And also by inhibiting the expression of pre pro TRH gene, T_3 decreases the TRH secretion from the hypothalamus. Reduced TSH, TRH levels decreases the thyroid hormone synthesis. Thus thyroid hormone regulates its own secretion. [39]

Role of iodide in the regulation:

Iodide itself is an important regulator of thyroid secretion. It has biphasic action. At low levels, thyroid hormone synthesis is directly proportional to the iodide intake. If the iodide intake exceeds 2mg/day it inhibits the thyroid hormone production by acting on the three steps of hormone biosynthesis - the iodide trapping, thyroglobulin iodination and the release. For that iodide is suppressing the activity of NAPDH oxidase, NIS and the TPO gene. This effect is transient one and it is known as ***Wolf Chaikoff Effect***. [7] But normal thyroid gland escapes from this effect as the intrathyroidal iodide level falls after 10 to 14 days. Sometimes in patients with multinodullar goiter, excess iodide can induce hyperthyroidism. This is called as ***Jod Basedow effect***. [7]

MECHANISM OF ACTION OF THYROID HORMONE



Mechanism of action of thyroid hormone

Thyroid hormone has action on almost all the tissues of the body. Like steroid hormones, it also has both genomic and nongenomic actions. [36]

Genomic Actions:

Thyroid hormone enters the cell via carrier mediated transport. Inside the cell T_4 is converted by 5' deiodinase into T_3. T_3 binds to the nuclear receptor present in the nucleus . In humans two thyroid hormone receptors(TR) genes are present. They are TRα and TRβ and their genes are located on chromosome 17 and chromosome 3 respectively. Each gene spliced to form two isoforms. TR α 1 & 2 and TR β 1&2 of which TR α_2 does not bind with T_3. Each receptors having ligand binding domain on the carboxyl terminal and DNA binding domain in the center with 2 cysteine zing finger. They are attached to Thyroid Response Elements (TRE). Regarding tissue distribution, cardiac and skeletal muscle predominantly contains TRα_1, whereas liver and kidney contains TR β_1. **TRβ_2 is expressed in pituitary, hypothalamus, cochlea and retina.** [7]

Thyroid receptors form dimerization with retinoic receptor(RXR). The unliganded TR-RXR complex bind with several co repressor proteins like NCoR (Nuclear receptor Co repressor) and

SMRT (Silencing Mediator for Retinoic Acid and Thyroid Hormone Receptor). When T_3 binds with the receptor complex the corepressors are released and co activators are activated and they promote histone acetylation results in large number of mRNAs followed by RNA translation leads to formation of new intracellular proteins. [36]

Non Genomic Actions:

Non genomic actions of thyroid hormone is independent of gene transcription. The actions occur within minutes in the plasma membrane, cytoplasm and mitochondria. The actions are effected by the interaction of thyroid hormone with certain enzymes like adenylate cyclase, Ca^{2+}ATPase and pyruvate kinase. Some of the non-genomic actions are oxidative phosphorylation, ion channels regulation, activation of cAMP 2^{nd} messenger system and protein kinase signaling cascades. [7, 36]

Physiological Actions of Thyroid Hormone

Calorigenic Action:

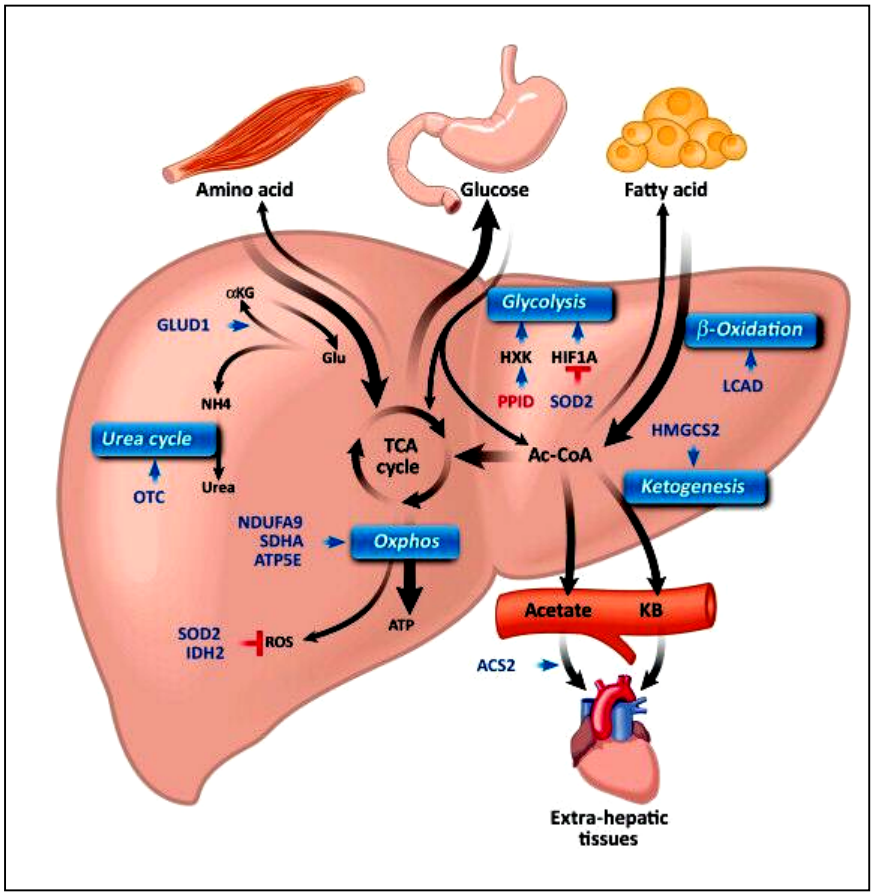
Thyroid hormone increases the basal O2 consumption in almost all tissues of the body except adult brain, Anterior Pituitary, spleen , lymphnodes, uterus and testes . Increased O2 consumption leads to excessive heat production. It is called as calorigenic or thermogenic actions of thyroid hormone. This is exerted by increasing the Na^+ - K^+ ATPase activity[37,39].

- T_3 increases the number, size and activity of mitochondria which in turn increases the ATP formation.
- Thyroid hormones regulate the oxidative phosphorylation by promoting the cytochrome oxidase activity and increasing the expression of uncoupler proteins like UCP-1,UCP-2 &UCP-3.
- The basal metabolic rate (BMR) is increased 60 to 100% of normal by the thyroid hormone. In completely athyroitic people the BMR is reduced to 40% of normal. [37]

Effects on Intermediary metabolism:

Thyroid hormone augments the expression of genes encoding the various enzymes involving metabolic pathways. There by it amplify all the intermediary metabolism. [7,36,37,39]

METABOLIC ACTIONS OF THYROID HORMONE



On Carbohydrate metabolism:

Thyroid hormone increases the absorption of glucose from the GIT and also the uptake of glucose by the cells. T_3 enhances the glycolysis and gluconeogenesis as well as the insulin secretion parallel to the increment in the plasma glucose. So the net effect is no substantial increase in the plasma glucose level. [26]

On Fat metabolism:

By stimulating the lipoprotein lipase enzyme T_3 accelerates the lipolysis and increases the free fatty acid concentration. But it lowers the plasma cholesterol concentration without increasing the metabolism. The possible mechanism is, thyroid hormone increases the number of hepatic Low Density Lipoprotein (LDL) receptors which removes the LDL rapidly and increases biliary secretion of cholesterol. [36]

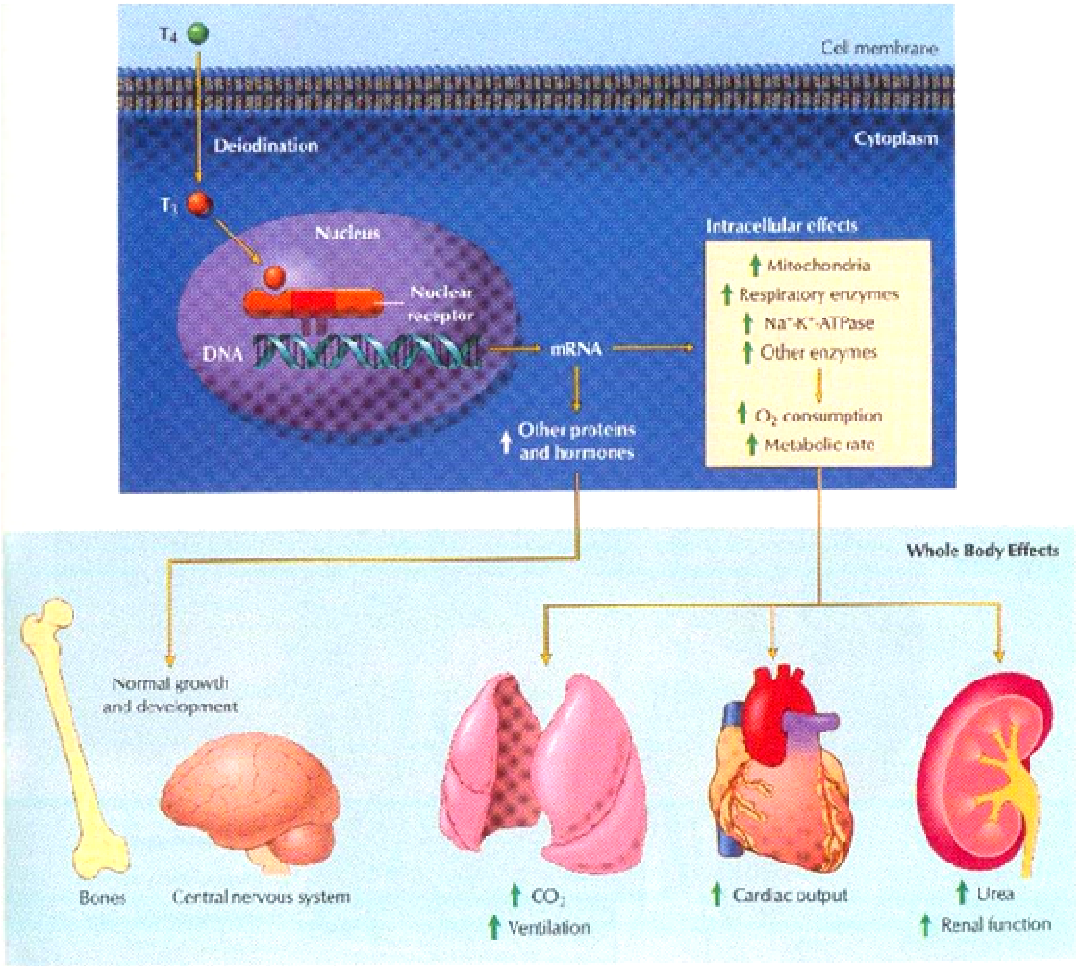
Effect on Protein Metabolism:

Thyroid hormone increases the protein turnover by promoting protein degradation. [7]

Effect on metabolic actions of other hormones:

It increases the effects of glucagon, cortisol, epinephrine, norepinephrine and growth hormone on the ketogenesis and proteolysis of the tissue proteins[34].

PHYSIOLOGICAL ACTIONS OF THYROID GLAND



Cardiovascular Effects:

Thyroid hormone increases the heart rate, myocardial contractility and thereby increases the cardiac output. Peripheral conversion of T_4 to T_3 doesn't takes place in the cardiac myocytes. So T_3 diffuses into the myocardium and exerts its action either directly or indirectly.

Direct Action :

It increases the expression of Myosin Heavy Chain α isoform, thereby increases the myocardial contractility (+ve ionotropic effect) directly.

Indirect Action:

It increases the responsiveness of the myocardial tissues to the catecholamine by increasing the β adrenergic receptors.

Blood Pressure (BP):

T_3 accentuates the transcription of Ryanodine Ca^{2+} channels which promotes the Ca^{2+} release from the sarcoplasmic reticulum and increases myocardial contractility during systole thereby increases the systolic BP.[36] It also increases the expression of Sarcoplasmic Reticulum Ca^{2+} ATPase pump which causes sequestration of Ca^{2+} and facilitates the myocardial diastolic relaxation. Because of +ve ionotropic effect the systolic BP is moderately elevated. Diastolic

BP is decreased by the thermogenic cutaneous vasodilatation and release more number of vasodilator metabolites into the blood and thereby decrease in the total peripheral resistance. [7,37]

Heart Rate:

T_3 increases the expression of β adrenergic receptors gene on the SA node and the AV node. Thus increases the Heart rate. [37]

Effects on Respiratory System:

Thyroid hormone maintains the normal arterial PO_2 & PCO_2 by enhancing the ventiltory response to the hypoxia and hypercapnia. [37]

Hematopoietic Effects:

2,3 DPG content is increased by T_3 and shift the ODC (oxygen dissociation curve) to the right thereby ensures the easy availability of O2 to the tissues. It induces the Erythropoietin production by the kidney resulting in increased red cell mass. [39]

Gastro intestinal effects:

Thyroid hormone enhances the appetite, food intake and reabsorption of glucose from GIT. It increases the gastric juice secretion, the bowel motility and decreases the transit time. [39]

Skeletal Muscle Effects:

Skeletal muscle requires adequate amount of thyroid hormone for their normal function. Because it increases the glycolysis and glycogenolysis and lowers the glycogen and creatinine phosphate concentration. Creatinine phosphate is essential for the conversion of ADP to ATP, thereby it regulates the energy production and storage in muscle.[7]

Effects on Renal System :

Thyroid hormone promotes the growth of the renal tubular epithelial cells. It increases the renal blood flow, GFR and also it enhances the reabsorption of electrolytes, glucose and water by renal epithelial cells.[37]

Effects on Reproductive Organs :

Thyroid hormone has a permissive role in the regulation of reproductive function in both sexes. In women it regulates the follicular development, maturation and ovulation. In males it promotes spermatogenesis and differentiation of pre pubertal cells.[7]

Endocrine Effects :

Thyroid hormone controls the other endocrine gland's actions. It increases the secretion of growth hormone from the pituitary somatotropes and decreases the prolactin secretion from the Lactotropes. Paratharmone , 1,25 dihydroxy cholecalciferol (Vit D) production is decreased by the thyroid hormone thereby prevents the bone resorption.[37]

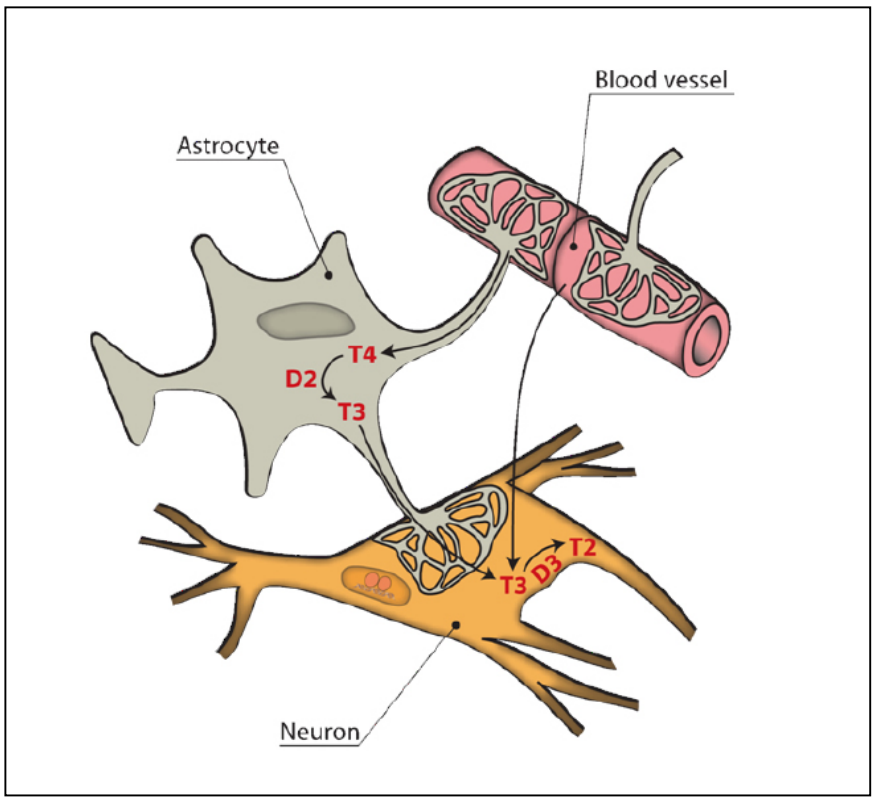
Effects on Musculo Skeletal System:

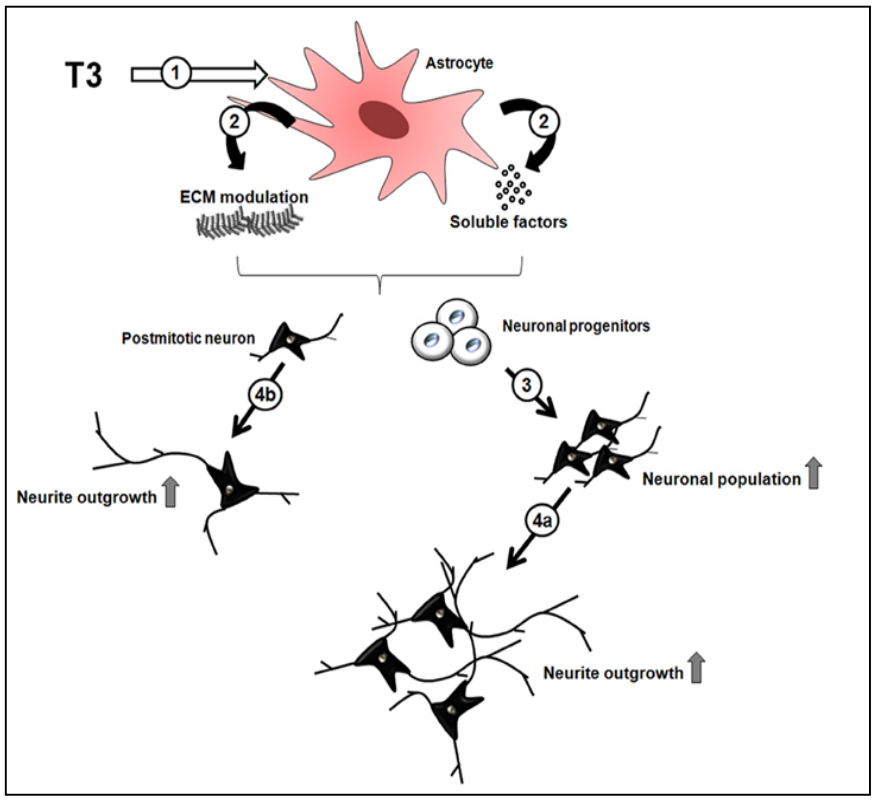
- Thyroxine stimulates the enchondral ossification and epiphyseal bone center maturation. During fetal life it enhances the maturation of chondrocytes in the cartilage.
- The eruption and development of the tooth depends on the thyroid hormone.
- It decreases the synthesis but increases the degradation of glycosaminoglycan (mucopolysaccharides) and fibronectin.[7]

CNS Effects:

Brain development maximally occurs in the last 6 months of fetal life and the initial 6 months of postnatal life. During this period adequate amount of thyroxine is essential because astrocytes contain type II deiodinase (D_2) which converts the T_4 into T_3 and executes following actions.[37]

ACTIONS OF THYROID HORMONE ON CNS





- It promotes the growth of the cerebral, cerebellar cortex and basal ganglia. It also increases the axonal proliferation, branching of the neurons, synaptogenesis, myelination and cell migration. [7]
- It promotes the synthesis of enzymes essential for the neurotransmitter production and also increases the number of receptors for the neurotransmitters.
- It enhances the myelin formation by inducing the glactosylsialyl transferase activity, thereby increases the speed of nerve impulse conduction.
- It increases the synthesis of protein and enzymes like succinic dehydrogenase and make avail the ATP for the nervous tissue function.
- By stimulating the reticular activating system, it promotes the wakefulness, alertness, awareness of hunger, learning and memory. [39]
- Adequate thyroid hormone is necessary for the normal emotional status of an individual.
- **Thyroid hormones are also important for the speed and amplitude of reflexes.** It shortens the reaction time of stretch reflexes like ankle Jerk or achilles reflex.

- **It plays a vital role in the development of cochlea.** So its deficiency leads to deaf mutism.[37]

Action on Auditory System:

Thyroid hormone has prominent effects on nervous systems through its role in gene expression, myelin production, neurotransmitter release, and axonal transportation. Likewise for the proper development of auditory system, adequate levels of thyroid hormones are required.[40] The exact mechanism of thyroid hormone role in the hearing is uncertain, the possible relationship is revealed by recent cellular level and molecular level experimental studies.

Morlies et al found that like other cranial nerves, VIII cranial nerve also has peripheral and central part. Thyroid hormone enhances the genes responsible for the myelinogenesis process and both parts undergo myelination simultaneously. In peripheral nervous system P0 (Peripheral Protein Zero), MBP (Major Basic Protein) are the genes expressed in schwann cells whereas in CNS along with MBP, PLP(Proteo Lipoid Protein) are expressed in oligodendrocytes for myelination. Thyroid hormone ensures the expression of all these genes in cochlea, brainstem, inferior colliculus and auditory cortex.[41]

TR β2 receptor proteins are present in the central intradural part of the auditory nerve. T_3 exerts its action via these receptors. Thus thyroid hormone accelerates the myelination process which is the prerequisite for the spreading of action potentials from the periphery to brainstem. The development of cochlea also requires adequate levels of thyroxine during fetal life. [41]

In the mechanism of hearing, the hair cells are the main structure involved in the transduction of sound waves into neuronal impulses. Thomas weber et al suggest that thyroid hormone acts as the first transcriptional regulator of the motor protein – ***Prestin*** in the ***outer hair cells***. It is related to sulfate / anion transport process. It is important for enhancing the amplitude and clarity of the sound. [42]

Brandt et al did a study using the patch clamp technique found that fast acting K^+ channels and calcium channels in the ***inner hair cells*** (IHC) require thyroid hormone for their activation and also observed the role of ***Otoferlin*** for the exocytosis of IHC. The developmental studies done on hypothyroid rats point out that, thyroid hormone is also necessary for the morphogenesis of cochlea and its structures. [43]

Hypothyroidism

Hypothyroidism is a group of clinical symptoms due to deficient thyroid secretion. It usually has an insidious onset and gradually progresses from asymptomatic subclinical hypothyroidism to severe form of myxedema coma.

Historical Review:

In 1874 English physician Sir Williams Withey Gull described the full blown expression of adult hypothyroidism . W M Ord named the condition as myxedema, because of the presence of mucin (myx-) in the skin and the subcutaneous tissue which leads to the swollen (edema) appearance. [26]

In 1882 Reverdin described that surgical removal of thyroid gland also produces similar clinical picture, and called as cachexia strumipriva. [44]

After Gulls description, enormous interest was aroused in myxedema. So London's clinical society formed a committee to study and report its results. Its report was published in 1888 and most of our knowledge regarding the etiology, clinical and pathological features of myxedema are based on that report only. [45]

In 1891 George Redmayne Murray was the person who first found that administration of the thyroid extract of sheep to the

myxedema patients provides good clinical response. But the active principle of thyroid hormone was first isolated in crystalline form by Edward Calvin Kendall in 1941. The chemical structure of thyroid hormone was clearly explained by Sir Charles Harrington in 1926. As the sheep thyroid extract is poorly absorbed, the levothyroxine sodium sulfate was identified and utilized for the treatment. [26]

Epidemiology :

Several epidemiological surveys depicted that hypothyroidism is one of the most common endocrine disorders. According to the update for primary care physicians data, about 1% to 2% of all adults once in their lives experiencing hypothyroidism. [46]

Every year 2.6 to 4.3% of Subclinical Hypothyroidism (SCH) cases progresses to clinical hypothyroidism. Middle aged Females are much more frequently affected by hypothyroidism. [45]

Regarding the prevalence of hypothyroidism the data have been obtained from the 20 year follow up study of Whickham survey, [47]

Prevalence	Women (per 1000)	Men (per 1000)
SCH	75	28
Hypothyroidism	18	1
Incidence	Women (per 1000/year)	Men (per 1000/year)
Hypothyroidism	4.1	0.6

Grades of Hypothyroidism:

The transition from the euthyroid to hypothyroid state is the initial step in the development of hypothyroidism. It occurs by decreased secretion of T_4 from the thyroid gland which causes feedback increased release of TSH from the anterior pituitary and maintains the T_4 levels within the reference range initially. Further decline in T_4 results in higher TSH values but T_3 levels are maintained by the conversion of T_4 to T_3.

When the T_4 level falls to very low value, the T_3 levels also fall. Thus the hypothyroidism gradually progressed from SCH , mild hypothyroidism to overt hypothyroidism. [48]

Grades	Thyroid state	TSH	f T_4	f T_3
I	SCH	Slightly elevated	Normal	Normal
II	Mild hypothyroidism	Moderately high	Low	Normal
III	Overt hypothyroidism	Very high	Very low	Low

The maintenance of serum T_3 concentration till the great fall in T_4 level serves to maintain the homeostasis of the metabolism.

Causes of hypothyroidism:

Hypothyroidism is caused by variety of functional and structural disorders of thyroid gland. Its severity depends on the duration of hormone deprivation. Based on etiology, it is broadly classified into, [39]

1.Primary hypothyroidism:

It is the inherent inability of the thyroid gland to secrete sufficient amount of its own hormones. It is otherwise called as thyroprivic hypothyroidism.

2.Secondary hypothyroidism:

This is due to defective secretion of TSH from the Pituitary or TRH release from the hypothalamus. Other names for secondary hypothyroidism are trophoprivic or central hypothyroidism.

3.Thyroid hormone resistance syndrome.

I. Primary (thyroidal) hypothyroidism: [28]

Congenital :

- Thyroid agenesis
- Mutation in genes encoding NIS and Pendrin
- Iodotyrosine halogenase deficiency
- Organification disorder (Thyroid Peroxidase deficiency)
- TSH receptor defects

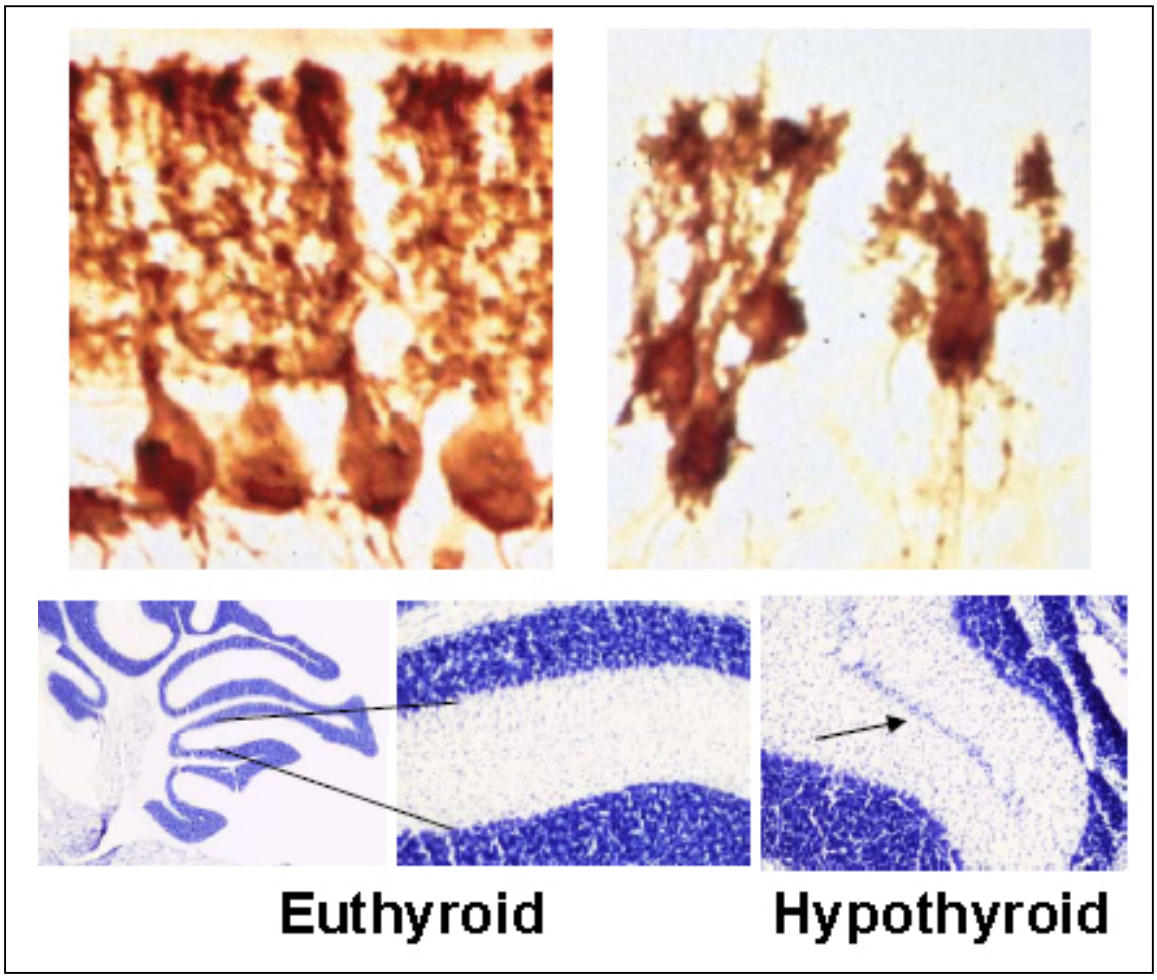
Acquired :

- Hashimoto's thyroiditis
- Endemic goiter (iodine deficiency)
- Iatrogenic
- Drug induced – Lithium, sulfonamide, iodide, Sunitinib, INFα
- Transient hypothyroidism:
    - Postpartum thyroiditis and Sub acute thyroiditis.

II.Central / Secondary (Hypothalamic Pituitary) hypothyroidism: [28]

- Tumors of pituitary , craniopharyngioma, meningioma
- Trauma – head injury
- Surgery
- I^{131} radiation

SYNAPTIC DENSITY



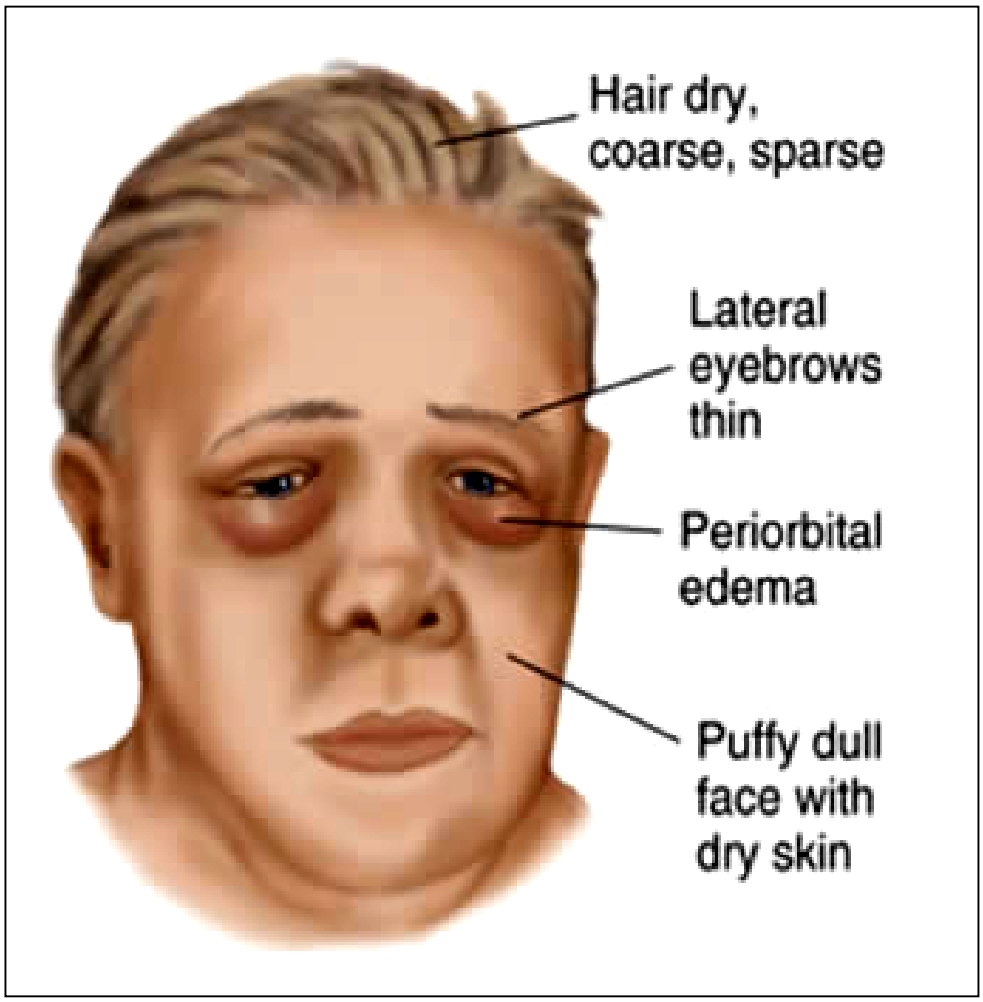
- Vascular – hemorrhage
- Infections – tuberculosis, abscess, syphilis, toxoplasmosis
- Functional defects in TSH biosynthesis – mutation of genes encoding TRH receptor, TSHβ subunit, pituitary transcription factors.
- Thyroid hormone resistance syndrome – mutations in genes encoding TRα TRβ, MCT8
- Consumptive hypothyroidism – massive infantile hemangioma.
- Infiltrative – Sarcoidosis, Histiocytosis, Hemochromatosis.

Pathogenesis of hypothyroidism:

Thyroid hormone deficiency affects almost all organ systems of the body. The characteristic pathologic finding is mucinous non pitting edema in the dermis. The mucinous material is the hydrophilic hyaluronic acid and glycosaminoglycan which attracts more water. Their excessive deposition is because of loss of thyroxine action on the degradation of mucopolysaccharides and fibronectin.[49] In the musculoskeletal system also the muscle cells are edematous.

In cardiovascular system the cardiac chambers are dilated or hypertrophied. The serous cavities contain abnormal amounts of fluid. The adrenals may be normal or it may show cortical

CLINICAL FEATURES OF HYPOTHYROIDISM



atrophy. Renal biopsy shows thickening of basement membrane and extra cellular deposition of amorphous material.

The brain shows gliosis, atrophy of neuronal cells. With longstanding myxedema, mucinous material is deposited in the neurons and form neural myxedematous bodies. It also produces neuronal hypoplasia and demyelination.[50]

Systemic Manifestations

Hypothyroidism Effects on Energy Metabolism:

Hypothyroidism reduces the basal metabolism of the body which in turn leads to decrease in the resting energy expenditure, oxygen utilization. It leads to low BMR, reduced thermogenesis and produces cold intolerance in hypothyroid patients. Because of fall in energy expenditure there will be net gain in body weight.

Increased adipose tissue elevates the leptin level, which increases the energy disposal and leads to reduction in adipose tissue. In hypothyroid patients plasma leptin level may be increased, or decreased or doesn't change.

A gastric peptide, Ghrelin also has a role in appetite stimulation and is elevated in hypothyroid patients. Serum visfatin and serum obestatin are increased in hypothyroidism whereas serum adiponectin and resistin concentrations doesn't change.[51]

Protein Metabolism:

Effect on protein metabolism is a complex one. Though hypothyroid state affects both the degradation and synthesis of proteins, a positive nitrogen balance only exists because the synthesis is affected more than the degradation. [26]

Carbohydrate Metabolism:

Impaired translocation of GLUT 4 transporters on the plasma membrane leads to decreased glucose uptake by the skeletal muscles and by the adipose tissue . Hypothyroidism reduces the rate of degradation of insulin, so the insulin requirement is reduced in diabetic patients with hypothyroidism. [28]

Lipid Metabolism:

Thyroid hormone deficiency reduces both the biosynthesis and lipolysis. The serum total cholesterol level is raised due to down regulation of the hepatic LDL – receptor which in turn increases the cholesterol secretion and biliary secretion of cholesterol. The LDL cholesterol is also elevated by non LDL receptor pathways.Friedrich and Pilger reported that no change in neuro – otological symptoms like dizziness, tinnitus and sensori neural hearing loss in hypercholesterolemia patients. [52]

SYMPTOMS OF HYPOTHYROIDISM	
Constitutional / general	**Fatigue, Weight gain, Cold intolerance, Hoarseness, Periorbital edema**
Cardiovascular	**Bradicardia, Diastolic Hypertension, Peripheral edema, Hyperlipidemia, Pericardial effusions**
Pulmonary	**Dyspnea, Pleural effusion**
Gastro intestinal	**Constipation**
Genito urinary	**Decreased GFR, Elevated creatinine, Infertility, Menorrhagia**
Dermatological	**Dry coarse skin, Diffuse alopecia, Yellow Skin**
Neurological	**Poor memory, Difficulty concentrating, Muscle weakness, Nerve entrapment syndrome, Delayed relaxation of deep tendon reflexes, Paresthesia, Impaired hearing , Psychosis.**

Cardio Vascular System:

- Hypothyroidism decreases the heart rate and stroke volume thereby decreases the cardiac output. It also causes cardiomegaly and pericardial effusion.
- ECG shows low voltage P wave and QRS complex, flattened or inverted T wave , prolonged PR interval and sinus bradycardia.[26,28]

Respiratory System:

- Prolonged duration of hypothyroidism causes weakness of respiratory muscles which leads to alveolar hypoventilation and CO_2 retention.
- 7% of patients show obstructive sleep apnea syndrome. Obstructive sleep apnea due to macroglossia, narrowing of pharynx due to soft tissue infiltration of mucopolysaccharides.[37]

Musculo Skeletal system: [28]

- Myalgia, muscle weakness, stiffness, cramps.
- Pseudo myotonic reflex or hung up reflex(delayed relaxation of deep tendon reflex)
- Carpal tunnel syndrome.

Digestive System: [36]

- Decreases the rate of peristalsis which leads to constipation. It causes fecal impaction in the colon and produces myxedema mega colon. As it decreases the contraction of gall bladder it may lead to Gall stone formation.

Haematopoietic System:

- Plasma volume, red blood cell mass and blood volume are decreased in hypothyroidism. Most of the patients suffer from mild normochromic normocytic anemia. Diminished reabsorption of vitamin B12 leads to Pernicious anemia. Megaloblastic anemia caused by reduced intestinal absorption of folic acid.
- Total and differential count of WBC is normal.
- Platelet count is normal but intrinsic coagulation pathway is defective due to decreased concentration of coagulation factors like factor VIII and IX.
- Coagulation tests showed that low factor VIII activity, low von Willebrand Factor, low or normal fibrinogen . [28]

Renal System:

- Decreased cardiac output leads to reduced renal blood flow, GFR and renal plasma flow.

- Serum uric acid level increases in postmenopausal women.
- Reduced renal ability to dilute urine which leads to increased serum creatinine and hyponatremia. [28]

Endocrine system:

Pituitary and Adreno cortical system: [25,27]

- Chronic untreated primary hypothyroidism results in thyrotroph hyperplasia and sellar enlargement. Increases the serum Prolactin concentration which may be associated with galactorrhea.
- The secretion of growth hormone decreased resulting in low serum IGF -1 concentrations.
- Hashimoto's thyroiditis may cause growth hormone deficiency. The response of insulin induced hypoglycemia to the plasma cortisol level also decreases.

Reproductive System: [28]

In adult men: Libido decreased. Reduced Sex hormone Binding Globulin (SHBG) leads to reduced serum total testosterone level but free testosterone is normal. Serum LH and FSH are normal, but their response to GnRH is diminished.

In adult women: Reduced SHBG leads to reduced serum estradiol and estrone concentration but free hormonal levels are normal. Hypothyroidism also causes irregular menstrual bleeding, reduced fertility, spontaneous abortion and preterm delivery

Nervous System: [28]

Though thyroxine is necessary for the development of CNS its deficiency leads to the following neurological symptoms not only in children but also in adult hypothyroid patients.

- Cognitive and behavioral deficits
- Head ache, poor memory , depression
- Slowdown of speech and movements
- **Deafness - neural or conductive type**
- Vertigo, tinnitus
- Thick slurred speech and hoarseness of voice
- Delayed relaxation of the deep tendon reflex leads to hung up reflexes
- **Low amplitude waves in EEG**
- **The absolute latencies and inter peak latencies of evoked potentials were prolonged.** [28]

HYPOTHYROIDISM AND HEARING LOSS

Sensory system involvement is more common among the hypothyroid patients. The threshold for special senses like smell, taste, visual and auditory impulses also altered. Among this hearing loss is one of the characteristic and most troublesome symptom. All types of hearing losses like sensorineuronal, conductive and mixed type of hearing losses have been reported. Vestibular abnormalities may be present. Adult type of acquired hypothyroidism must be differentiated from the sensorineural hearing loss of Pendred syndrome. Because thyroid hormone treatment provides complete cure to the acquired hypothyroidism, not to the Pendred syndrome.

- In 1907 – Kemp was the first person who demonstrated the Sensory Neural Hearing Loss (SNHL) in Hypothyroidism and found that it can be reversed by administering the thyroid extracts. [16]
- Audiometrical documentation of Hearing Loss in acquired hypothyroidism was first done by Hilger. [16]

Incidence of deafness in hypothyroidism:

The exact incidence of deafness in hypothyroid patients varies from study to study.

Vikas Malik from India by a study based on pure tone audiometry, reported that 11.5% to 95% of cases have hearing loss in hypothyroid individuals. [13] A study on hearing profile in hypothyroidism found that 46.9% conductive hearing loss, 28.1% of SNHL and 25% cases of mixed type of hearing loss.

Chandrasekar M et al reported that 86% of mild bilateral hearing loss, 48.8% mild hearing loss and 40.62% moderate hearing loss among hypothyroid patients who are not on treatment. [17]

Causes of Hearing Loss:

Even though so many studies have been done to see the association of symptom complex and the hypothyroidism, still the association is poorly understood. The possible mechanisms are,

Conductive Hearing Loss(CHL):

According to Meyerhoff et al glycogen deposition causes structural damage to the tympanic membrane and partial obliteration of oval or round window which may be the reasons for CHL in hypothyroidism.[40] Hypertrophy of the mucosal lining of the Eustachian tube and middle ear can also be a possible mechanism. [13]

Sensorineural Hearing Loss (SNHL):

Adequate levels of thyroid hormone is necessary for the development and maturation of auditory system. So far it was known that Progesterone was the only hormone having influence on

nerve conduction. Now it was identified that thyroid hormone also plays a main role in the myelinogenesis process.[53] Myelinogenesis process involved the expression of myelin genes and the sequential myelination of nervous system.

Thyroid hormone ensures the glial gene expression in the auditory system. TRβ is very much important for the myelination of auditory nerve. In humans the auditory system attain full maturity at birth. Adequate levels of thyroid hormone is vital for the synchronized nerve impulse transmission at the onset of hearing. It was identified that even after the onset of audition the myelination of auditory pathway takes place. So not only the congenital hypothyroidism, adult onset hypothyroidism also affects the myelination and leads to delayed conduction along the brainstem auditory pathway.[54]

Abott et al proposed that diminished myelination and cerebral hypo metabolism may be the reason for SNHL.[55] According to Cuddon et al, axonal degeneration may be the cause for SNHL.[17] Knipper et al found that thyroid hormone is essential for the myelination of auditory pathway and maturation of auditory system.[43]

TUNING FORK TESTS

WEBER'S TEST

RINNE'S TEST

Parving et al in 1983[23] and Isam et al n 2001[24] were found that SNHL was the predominant type of hearing loss in the hypothyroid people.

Hypothyroidism - Diagnosed by,

Thyroid profile

- Serum TSH,
- Serum free T3
- Serum free T4.

Tests for Hearing Loss ,

- Rinne's test
- Weber's test
- Absolute Bone Conduction Test
- Pure tone audiometry
- Tympanometry

Electro physiological studies:

- Electrocochleogram
- Brainstem auditory evoked response (BAER)
- Transient acoustic emission

Among the electro physiological studies BAER is an useful noninvasive, objective type of study helps to assess the integrity of the brainstem auditory pathway . [56]

EVOKED POTENTIAL

The advancement in the computer signal processing, the electrophysiological studies gain their place in the medical diagnostic field. It has become a useful, objective clinical method in assessing the central nervous system, peripheral nerves and muscles. Evoked potential is, the electrical manifestations of brain's responsiveness to the external stimulus. Averaging techniques have been utilized for recording the neuroelectric responses for the diagnosis of neurological disorders like neuropathies and intracranial tumors. The clinical utility of Evoked Potentials is based on their ability, [57]

- To demonstrate the abnormal nerve conduction in sensory system.
- To explore the subclinical involvement of the nervous system.
- To define anatomic locations of the disease processes like demyelination.
- To monitor the neurological status of the person.

In theoretical aspect any sensory modality can be tested, but in our routine clinical practice, following tests are being done frequently, [57]

- Pattern reversal Visually Evoked Potential (PR VEP)
- Short latency Somato Sensory Evoked Potential (SSEP)
- Brainstem Auditory Evoked Potential (BAEP)

Historical Review: [56]

Since the early 1950s evoked potentials have been utilized in the patients with neurological disorders, but it was only in 1970s they gain a definite clinical utility. The history of development of the evoked potentials is closely related to the discovery of electricity.

- In 1752 - Benjamin Franklin discovered the presence of two opposing forces of electricity that is positive and negative.
- In 1791 – The fact that the nerves are good conductors of electricity was discovered by Luigi Galvani.
- In 1850 - Helmholtz measured the conduction velocity of nerve in frog.
- In 1929 – Hans Berger recorded the spontaneous electrical activity from the scalp. It was the first human electroencephalogram (EEG).
- In 1939 – Davis was the first person who noticed the electrical potentials on the human skull in response to repeated auditory stimulation. That potentials are initially called as " V" potentials or vertex potentials. These potentials are very small and difficult to measure.
- In 1951 – Dawson described the averaging techniques for the detection of small evoked potentials .

- In 1967 – Sohmer and Feinmesser showed the placement of surface electrodes on the ear lobe and the vertex. They were the persons who recorded the BAEP initially.
- In 1971 – Jewett and his associate Williston described the human BAEP wave forms and named the peaks with roman numerals I to VII. The wave forms are called as **Jewett bumps.**[58]
- In 1975 – Starr and Achor proposed the BAER changes in neurological disorders.
- In 1994 – Moller identified that Inferior Colliculus is the waveform generator of the wave V.

Types of Auditory Evoked Potential (AEP):

Auditory Evoked Potentials generated in the brain can be classified according to the latency , [59]

- Short Latency Auditory Evoked Potential with latencies <10ms.
- Long latency Auditory Evoked Potential with latencies >50ms
- Middle Latency Auditory Evoked Potential with intermediate latencies.

Middle and Long latency Auditory Evoked Potentials are generated within the cerebral cortex. So they are used for the assessment of cognitive functions. Short latency Auditory Evoked Potential generated in the brainstem is called as BAER. [59]

Brainstem Auditory Evoked Response (BAER) :

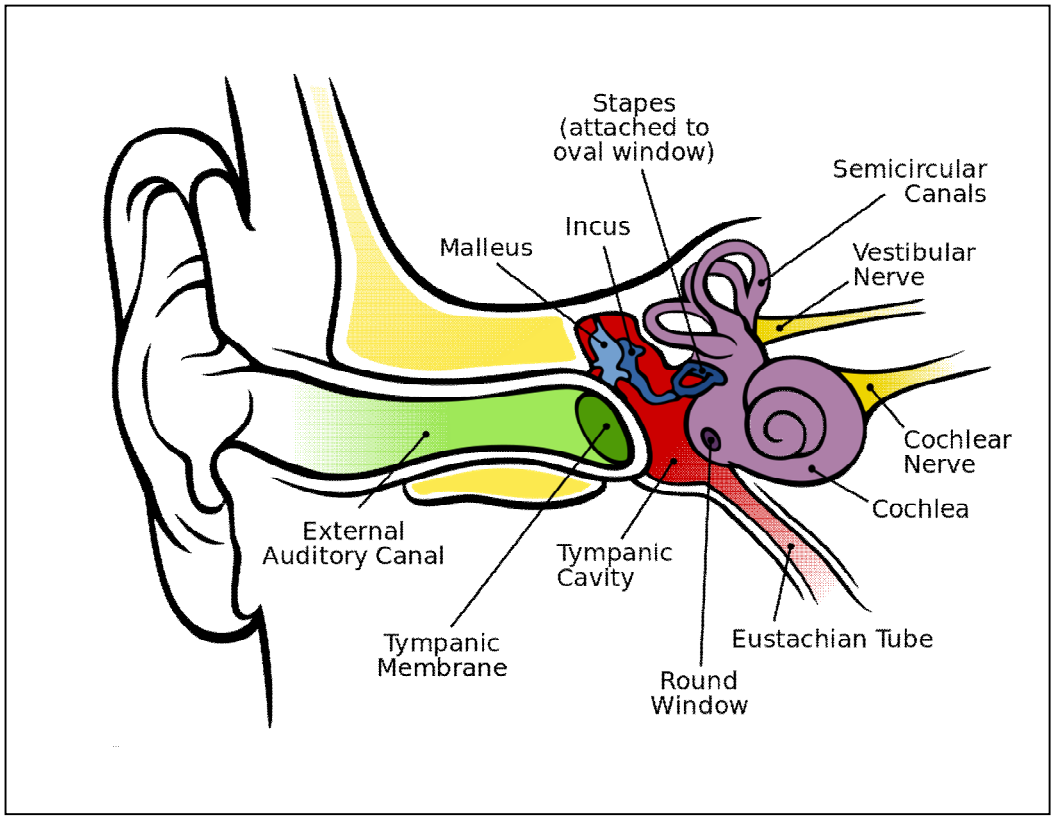
BAER is short latency auditory evoked potentials, which occurs within 10 to 15 milliseconds of an acoustic stimulation. Otherwise known as Auditory Brainstem Response (ABR) or Brainstem Auditory Evoked Potentials(BAEP). It helps to find the functional integrity of the central auditory pathway which includes VIII cranial nerve, Pons, and Midbrain. It can be used for[59,60] ,

- Screening of Hearing loss and Hearing threshold estimation in difficult to test population like infants, children and psychiatric patients.
- Differentiate between peripheral and central nervous system abnormalities.
- Confirmation and localization of brainstem dysfunction.
- Intra operative monitoring.

Anatomical and Physiological Basis of BAER: [7,25,34,36]

The human ear is not only an organ of hearing, but also an organ of equilibrium. The auditory system consists of two major portions: the peripheral auditory system and the central auditory system which function together to transmit, transduce, propagate and analyze the auditory stimuli.

ANATOMY OF EAR

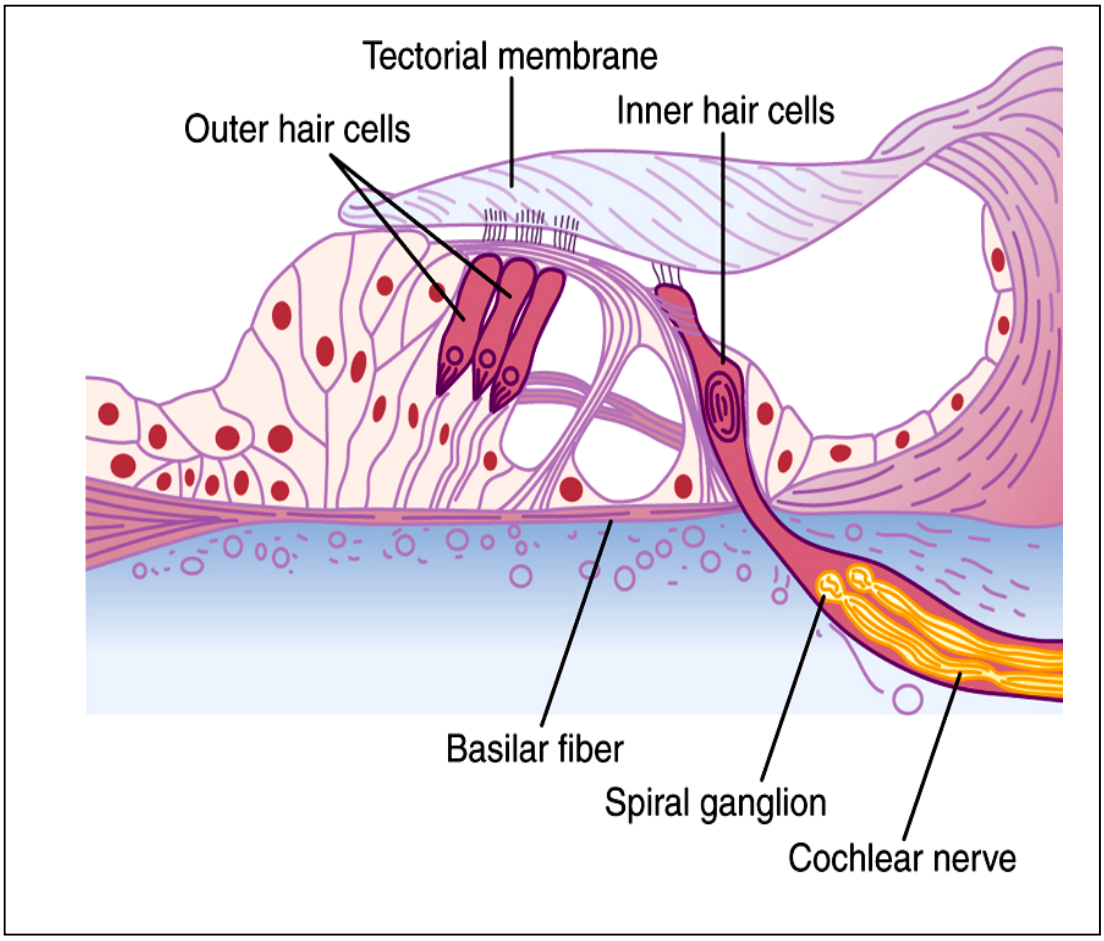


Peripheral Auditory System:

Human ear is made up of three parts: the external ear, middle ear and inner ear. The external ear consists of pinna and external auditory canal. The pinna directs the sound waves into auditory canal thereby it is helpful for the sound localization[25]. The external auditory canal ends at the thin transparent membrane called tympanic membrane or eardrum. The canal's main function is to transmit the sound pressure waves to eardrum which has a resonant frequency of about 3500Hz.[7]

The middle ear opens through the Eustachian tube into the nasopharynx. It contains a chain of ossicles that connect the tympanic membrane to the oval window and transmits sound waves to inner ear.[36] The inner ear consists of the cochlea (auditory component) and the semicircular canal (vestibular component). The cochlea is a snail shaped coiled tube which makes 2 ¾ turns around a central bony structure called modiolus. The cochlea is divided into three compartments by two membranes – the Reissner's Membrane and the Basilar Membrane.[7]

ORGAN OF CORTI



The three compartments are, scala vestibuli, scala media or cochlearduct and scala tympani. The scala vestibuli and tympani contains perilymph whereas the cochlear duct is filled with endolymph. The organ of corti rests with its hair cells on the basilar membrane which forms the floor of scala media.[7] The chief sensory receptor for hearing are 2 types of hair cells. They are,

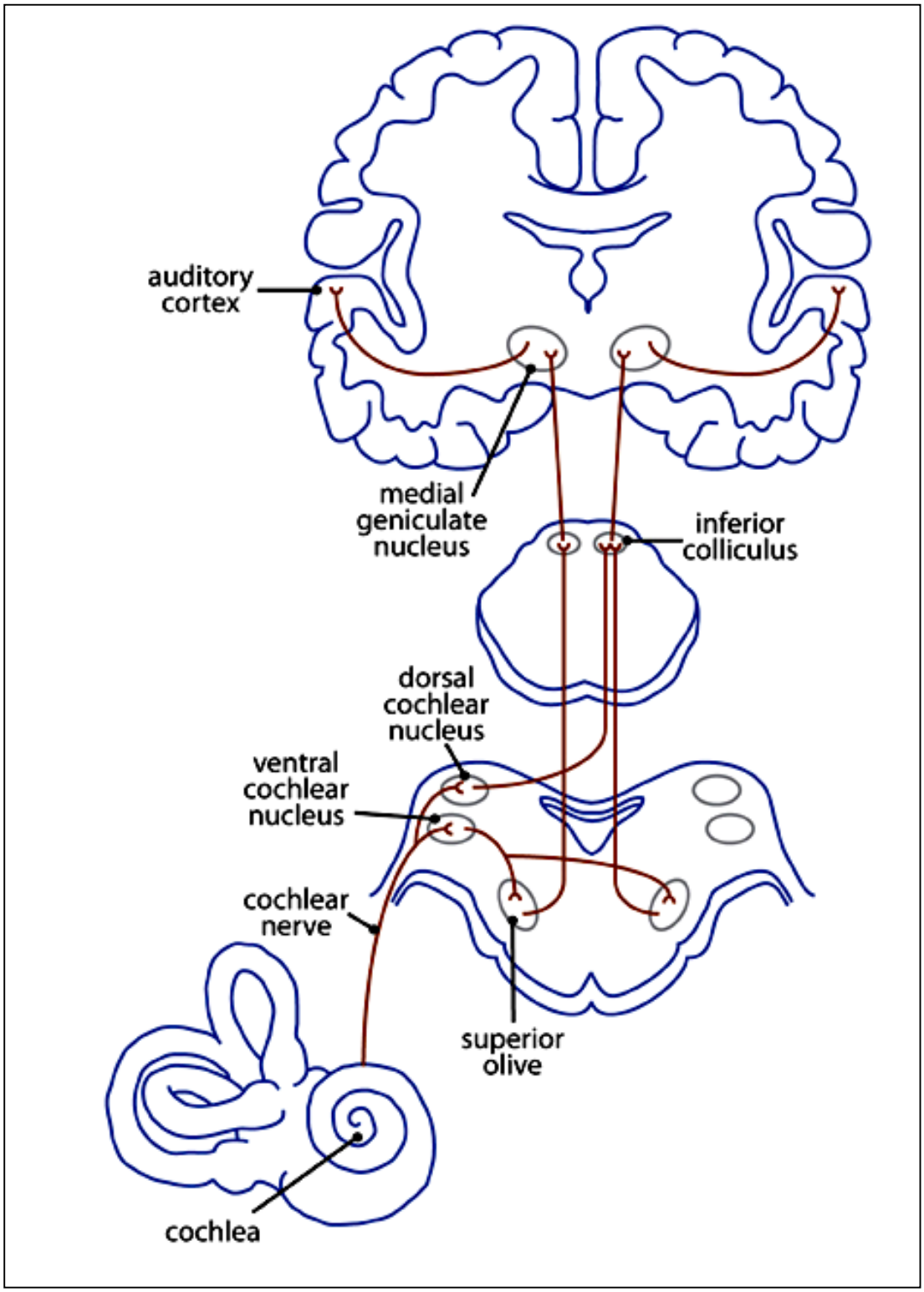
i. Single row of inner hair cells (IHC)

ii. Three rows of outer hair cells (OHC)

The cilia of outer hair cells project into thin gelatinous tectorial membrane. The inner hair cells generate action potential in the auditory nerve, thus it acts as a primary sensory receptor for hearing. The outer hair cells have different function, it responds to the sounds, depolarization causes shortening and hyperpolarization causes lengthening of outer hair cells. It helps to amplify the amplitude and clarity of sounds. This changes attributed to **prestin** a membrane protein in the outer hair cells.[34]

The basilar membrane is shorter (100µm) near the base and wider (500µm) at the apex of the cochlea. High frequency tones produce maximum movements near the base whereas low frequency tones near the apex. Thus basilar membrane acts as frequency analyzer. It was proposed by Von Bekesy. The hair cells are innervated by dendrites of bipolar cells and their axons form the cochlear nerve.[7]

AUDITORY PATHWAY



Central Auditory Pathway: [34,36]

Axons of the bipolar cells in the spiral ganglion forms the cochlear division of the VIII cranial nerve. These axons synapse in the cochlear nucleus. The Cochlear nucleus is divided into two subnuclei,

- Dorsal Cochlear Nucleus (DCN)
- Ventral or Accessory Cochlear Nucleus (VCN)

The VCN is further subdivided into,

- Antero Ventral Cochlear Nucleus (AVCN)
- Postero Ventral Cochlear Nucleus (PVCN) [62]

Tonotopic organization is found in cochlear Nucleus:

Axons of the lower frequencies from the spiral ganglion cells project to the DCN and the AVCN. The higher frequency organ of corti hair cells project to the AVCN and DCN. The axons from the mid frequency end up between two extremes. Thus the frequency spectrum is preserved. [7]

The output from the AVCN passes through the ventral acoustic stria which forms the trapezoid body and it terminates in superior olivary nuclei(SON) and inferior colliculus. The projections from the PVCN mostly go via the ventral and middle acoustic stria to terminate in superior olivary nuclei and inferior colliculus.

The DCN forms the dorsal acoustic stria which terminates in superior olivary nuclei and the contra lateral inferior colliculus. [62]

Superior Olivary Complex:

Superior Olivary Complex has medial and lateral components. The medial component receives excitatory input from both sides AVCN. The lateral component receives inhibitory inputs from the contralateral AVCN and PVCN and excitatory inputs from AVCN and PVCN via trapezoid body. Thus the differences in the activity of neuron provide the information about the source of the sound. Binaural interactions are occur at the level of superior olivary nucleus which is important for the directional localization of sound. [7]

Lateral Lemnisci : From the superior olivary complex the fibers project to ipsilateral and contralateral lemnisci. Each lateral lemnisci ascends along the dorsolateral brainstem upto the midbrain.

Inferior colliculus : In the midbrain most of the fibers terminate in the inferior colliculus.

Medial geniculate body: From there the fibers end in the Medial geniculate body of the thalamus. [34,36]

Auditory cortex:

From the thalamus auditory radiations project to the superior gyrus (Heschl's gyrus) of the temporal lobe which is the auditory cortex (area 41 & 42). Some fibers project to the association cortex in the tempero parietal region (areas 20, 21,22).

Cortical Organization:

Like those of other primary sensory areas, the primary auditory cortex has sensory maps in addition it has tonotopic maps. Neurons present in the primary auditory cortex form the isofrequency columns as well as alternating columns of summation and suppression columns.

- Isofrequency columns - have the same frequency
- Summation columns - more responsive to binaural input.
- Suppression columns - more responsive to monaural input. [7]

Frequency threshold:

The audible range of human ear is 20Hz to 20,000Hz. The human ear is most sensitive to 1000 to 4000Hz range. The pitch of the average male voice is 120Hz and the female voice is 250Hz. [34]

Mechanism of Hearing

The sound travels through the air and it reaches the external ear. It transmits sound waves along the auditory canal to the tympanic membrane and vibrates it. In turn vibrations conducted along the ossicular chain up to the oval window of cochlea. The middle ear matches the impedance of energy from external ear to inner ear, because the external ear transmits through air and the cochlea through the fluid. Some amount of energy will be lost as a result of resistance. But this system raises the sound pressure that reaches the oval window by lever action of the ossicles (1.3 times) .[34] It raises the efficiency of sound energy transfer by 30dB in the range of hearing from 300 to 3500Hz. [7]

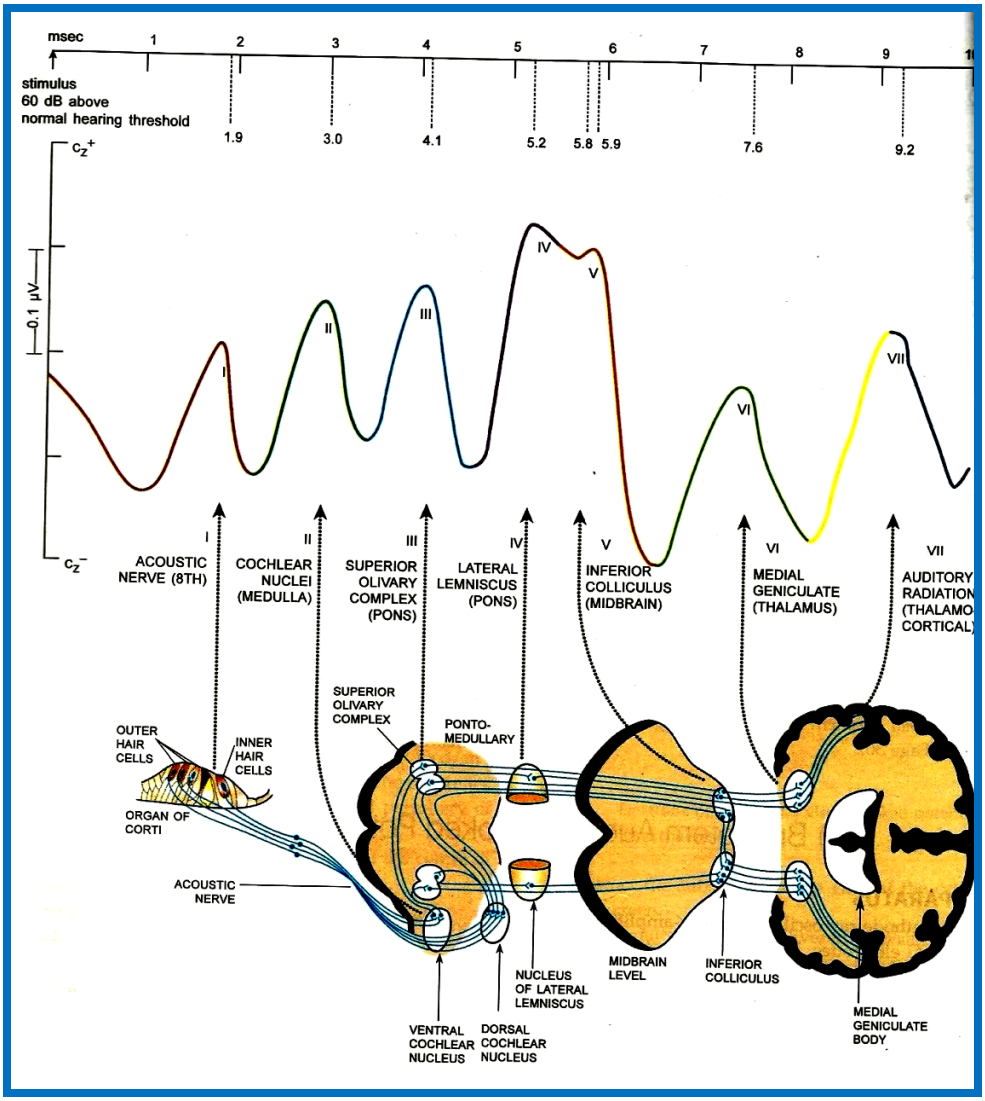
From oval window the sound vibrations are transmitted through the scala vestibuli and tympani which contains perilymph. Then these vibrations are passing through the Reissner's Membrane into scala media to the basilar membrane. This sets up travelling wave along the basilar membrane which stimulates hair cells in the organ of corti. The bending of stereo cilia of hair cells towards the tallest cilium and causes depolarization of hair cells. This leads to the release of neurotransmitter especially Glutamate, which initiates the other neighbor afferent neuron depolarization and generate receptor potentials. [34]

Once the action potentials are generated in the hair cells, the impulses are transmitted through the auditory nerves to the cochlear nucleus which is the termination of all fibers of the auditory nerve. From the cochlear nucleus the second order neurons project to the superior olivary complex via the trapezoid body. The tonotopic organization is maintained in the cochlea and the superior olivary Nucleus. From there third order neurons transmits the impulses through the lateral lemniscus, medial geniculate body up to the auditory cortex via auditory radiations. [36]

Brainstem Auditory Evoked Response:

The BAER, a series of short latency, subcortical, far field electrical potentials which provide noninvasive measure of the potentials from the VIII nerve, pontomedulary, pontine and midbrain portion of the auditory pathway. These are volume conducted evoked potentials which can be recorded by using electrodes placing on scalp. There are five, sometimes seven distinct waveforms are recorded within 10 to 15 milliseconds of the auditory stimulus, labeled I to VII in roman figures. [56]

WAVEFORM GENERATORS



Wave form Generators[56,60,63,64]

Wave I:

It is originated from the peripheral portion of the cochlear nerve. It is recorded from the stimulated ear and virtually absent from the contralateral ear. It is necessary to calculate the central auditory brainstem conduction time. [60]

Wave II:

It has two separate components, generated either from the intracranial portion of the cochlear nerve or the cochlear nucleus. It is attributed to the change in the volume conductor between the inside and outside of the internal auditory meatus. It is not commonly used in clinical interpretation of BAEPs. [63]

Wave III:

By the intra operative recordings it is found that wave III produced from the Pons. Muller and his associates found that, superior olivary complex in the caudal pons is the primary generator of the wave III and some contribution from the trapezoid body. It is present with equidistant between waves I and V. It may have bifid pattern which makes it difficult to identify. [64]

Wave IV:

It has same peak with wave V and it is generated by the nuclei of Lateral lemniscus in the upper pons. Muller and his associates found that wave IV requires intact ventral nucleus of the lateral lemniscus[62].

Wave V:

It reflects the activity of multiple anatomical structures of auditory pathway. Wave V is originated from the vicinity of inferior colliculus. More than 99% of the axons of the lower auditory brainstem region, are going through the lateral lemniscus to the inferior colliculus. By the transverse section experiment it is found that intact inferior colliculs is required for the wave V. [56]

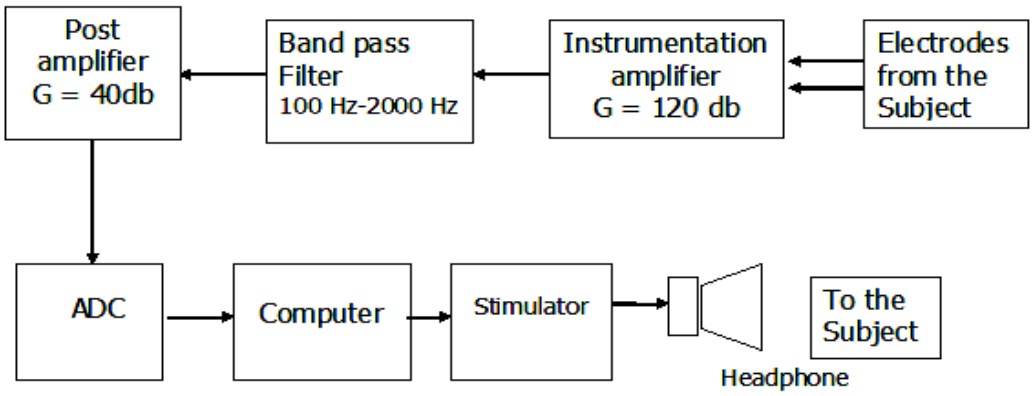
Wave I, wave III and wave V are constant reproducible , robust components of BAEP complex, which are clinically very much useful. [56,65]

Wave VI and VIII :

They can be seen in some individual traces. They are present in 70% of normal BAEP but poorly reproducible. Their origin is unclear and less helpful clinically. It has been suggested that the wave VI and VII originated from the medial geniculate body and auditory radiation.[56]

BAER Recording Technique

The guidelines for clinical and intraoperative recordings of BAER was proposed by American clinical neurophysiology society, 2006a and American Electroencephalographic society 1994 respectively. [59] The BAER amplitudes are in the sub microvolt range. It is much weaker than the surrounding environmental noise, background electro cerebral activity and muscle activity. Hence BAER recordings require special amplifiers called bio amplifier to make these signals large enough for further signal processing, filters for filtering the undesirable electrical activity, digital converter for converting the scalp recorded electrical activity to binary format that can be utilized by a digital computer and a signal averager. [65]



Stimulus :

A mixed frequency of broad band clicks (100 to 8000Hz), using the acoustic energy over a wide range of audio frequencies can be used for the neurologic evaluation. Clicks are single monophasic square wave pulse delivering for 100μsec duration by using a standard audiometric ear speaker. These clicks stimulates a large number of neurons which fired simultaneously and produce a larger response. [59,66]

Stimulus polarity :

Based on the type of pressure applied to the tympanic membrane three types of stimulus polarities are present. They are,

- Rarefaction click
- Condensation click
- Alternating polarity

The clicks in which first and most prominent acoustic wave creates a positive pressure and displays the tympanic membrane outwardly is referred to as **rarefaction clicks** . The clicks in which the acoustic wave creates a negative pressure and displays the tympanic membrane inwardly is called as **condensation clicks**. **Alternating polarity** is the clicks which creates alternating negative and positive pressure and displaces the tympanic membrane inwardly and outwardly. [60]

For optimal recording and resolution of wave I rarefaction click polarity is the best and it is used widely in clinical recordings. [59]

Stimulus Intensity: [59,60,66]

The stimulus intensity must be loud enough to elicit a clear BAER waveform without causing ear discomfort. 60 – 65 dB above the sensation level of the subject is optimum intensity. Reduced stimulus intensity is used for assessing the wave V latency. High stimulus intensity is used for neurologic diagnosis. Shift of the stimulus intensity to higher level without change in its shape suggests Conductive Hearing Loss while change in the shape of the curve with increased slope suggests Sensorineural Hearing Loss. [59]

Stimulus Rate:

Stimulus rates are widely vary from 5 to 200 / sec. Stimulus rate of 8 – 10/sec is optimum for clean resolution of short latency BAER. For individual peak identification stimuli rate of 10 – 15 / sec are used, whereas for threshold testing higher rates are used for measurement of wave V latency. Higher rates of stimulation reduce the amplitude of BAER. [59,66]

Monaural Vs Binaural Stimulation:

Acoustic stimuli should be delivered monaurally, i.e., one ear is stimulated at a time and responses are recorded from the same ear. It prevent the influence of abnormal or absent response to the stimulation of the other ear. [67]

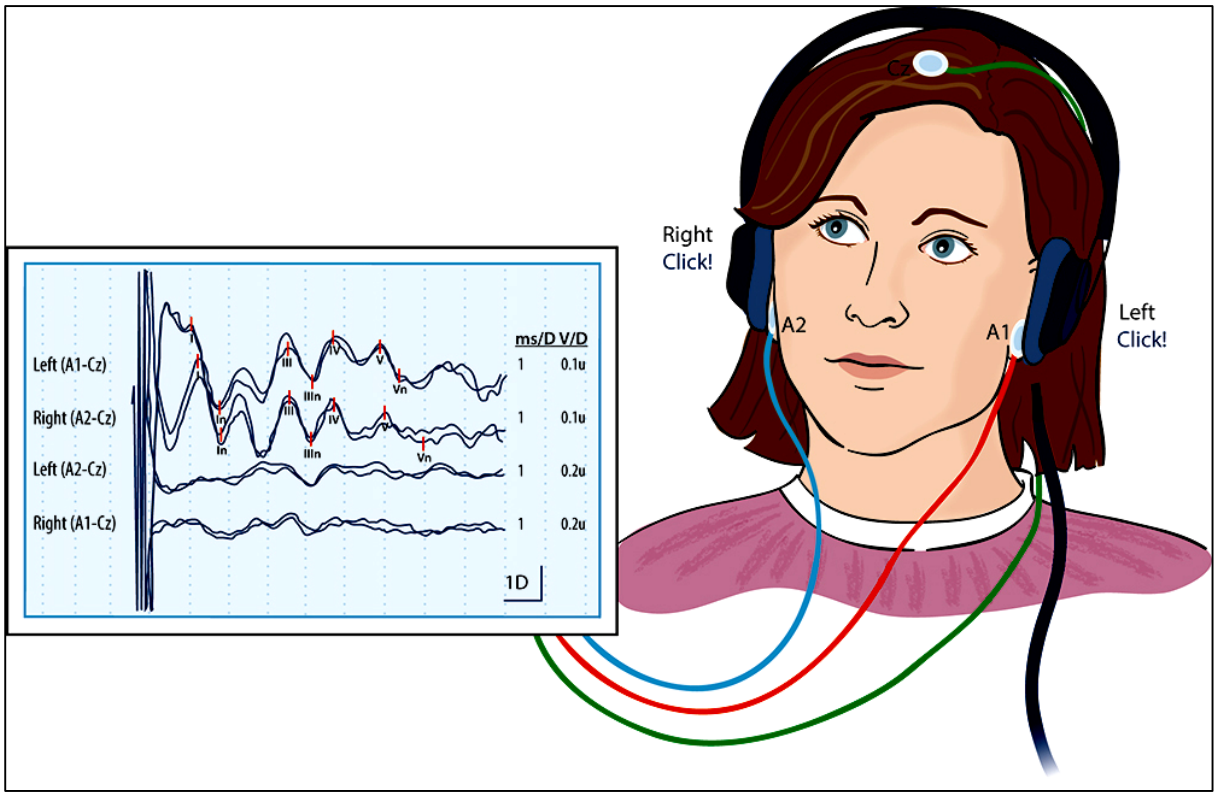
Contralateral Masking:

To eliminate the acoustic crosstalk that is bone conducted responses, the contralateral unstimulated ear is masked by white noise at 60dB SPL(sound pressure level) is used. Systematic masking of the unstimulated ear is recommended for useful precaution in routine BAER recording. [59,60]

Recording Procedures:

Subject should be investigated in a quiet room, supine or recumbent position for the optimum relaxation of neck and face muscles. An electrically shielded room is never needed and sound proofed room is not always necessary. It can be recorded during either wakefulness or sleep. Sedation can be used in very young or tense patients. Because BAER unaffected by sleep, anesthesia and even doses of barbiturates sufficient to induce coma. [68]

ELECTRODE PLACEMENT IN BAER



Electrode placement and Montages:

BAER recorded between the vertex and both earlobes or mastoid process. The surface electrode in the form of disc is most commonly used in clinical practice. It is made up of silver, gold, platinum and stainless steel. Silver or gold electrodes have stable electrode polarization potentials which results in noise free recording. After careful skin preparation, the electrodes are pasted by using standard electrode paste according to the international 10 – 20 system of EEG electrode placement. [59]

The positions are,

- The scalp electrode placed at the vertex (Cz)
- The recording electrodes placed at the both ear lobes (Ipsilateral Ai & contralateral Ac) or mastoid process(Ipsilateral Mi & Contralateral Mc)
- The ground electrode can be placed anywhere in the body, for convenience mostly in the forehead (Fz).

Electrode impedance should be kept less than 5 kOhms. [56]

Montage :

Generally two channel montage system is suitable for most clinical situations.

Channel 1 - Ipsilateral ear lobe Ai or mastoid Mi - Vertex Cz

Channel 2 - Contralateral ear lobe Ac or mastoid Mc - Vertex Cz

As BAER are far field potentials, little displacement of the recording electrodes do not significantly alter the BAER waves. Exception is wave I - which is the near field potential, is generated from the peripheral portion of auditory nerve. [63]

Amplification:

The raw analog data must be amplified by high input impedance differential bioamplifier with the rejection ratio of at least 80 dB (10,000:1). Thus it amplifies about 50,000 or 100,000 times. [59]

Filter :

It allows a particular range of frequency from a signal. It is required for eliminating the noise and bringing out the characteristics of the waveforms.

- The low frequency filters – it is otherwise known as high pass filter. Because it remove the slowly changing components up to 100Hz and allows the higher frequencies to pass through.

- The high frequency filters - it is also called as low pass filters. It removes the rapidly changing higher frequency components and allows only the low frequencies.

The recommended band pass filter is about 30 to 3000Hz. In clinical application, low frequency cut off is < 300Hz , high frequency cut off is >3kHz. [68]

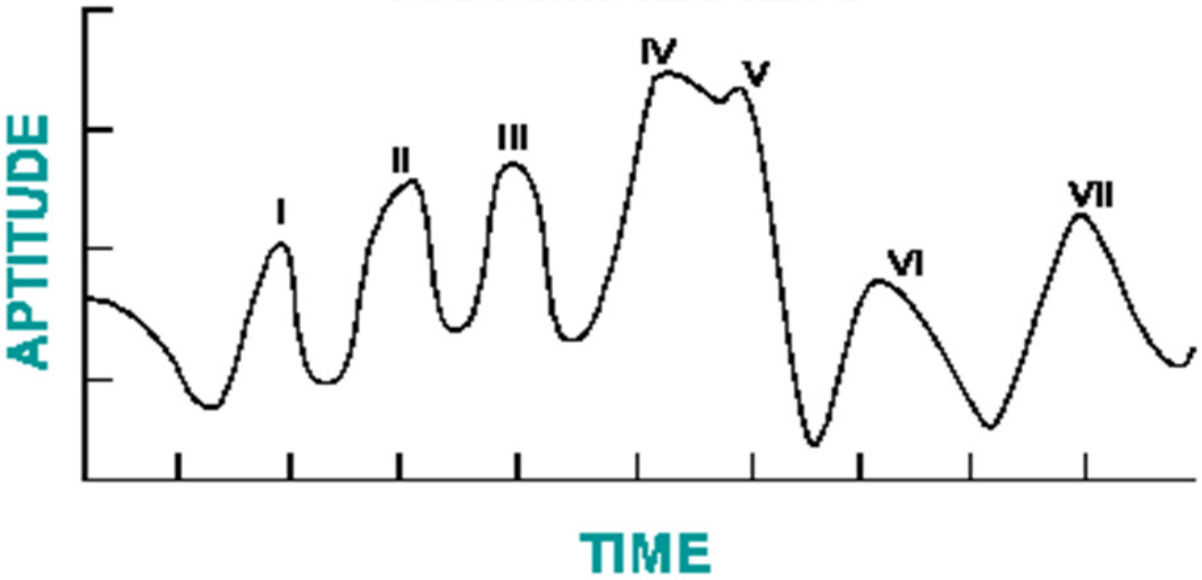
Signal Averaging :

It extracts very small signals which are buried in large noise. Back ground noise is reduced through averaging and filtering. Generally 1000 to 4000 stimuli is used in averaging to form a clear resolution of BAER. By averaging the time locked signals, the small signals become prominent and stored. Randomly occurring noise is cancelled out. [66]

Sensitivity and Sweep Speed:

The duration and latency of evoked potentials is influenced by sensitivity and sweep speed. If the sweep speed increases, it results in shortening of latency. Two or more response can be obtained and superimposed to demonstrate the replicable nature of their components. The sweep rates are increased or decreased based on signal to noise ratio.

NORMAL BAER



NORMAL VALUES OF BAER LATENCIES

BAER	Mean(ms)	SD (ms)
Absolute Latencies		
Latency I	1.5	0.17
Latency III	3.8	0.15
Latency V	5.6	0.20
Inter peakLatency		
IPL I – III	1.6	0.20
IPL III – V	1.7	0.20
IPL I - V	3.9	0.20
Right - Left difference I- V	0.17	0.10

The averaged results displayed on an oscilloscope to monitor artifacts. The amplitude of the stored data can be amplified by increasing the sensitivity. [63]

Analysis of Results:

- The Amplitude (measured from peak to trough)
- Latency (the time between the stimulus and the particular peak)
- Inter Peak Latency (the time between peaks)
- Inter aural latency (difference in wave latency between both ears)
- Wave V/I amplitude ratio.

The patient values are compared with the control population who are neurologically and audiologically normal, in whom the BAER recorded using the same stimulation rate. [59,63]

Wave Inter Peak Latencies (IPL): [56,60,63]

I – III IPL:

It is a measure of conduction from VIII nerve across the subarachnoid space into lower pons. It is affected by tumor, inflammation, or diseases affecting the proximal portion of the auditory nerve. Its upper limit is 2.5ms with the right to left side

difference is less than 0.5ms. The prolongation of I – III IPL is usually associated with I – V IPL prolongation.

III – V IPL:

It is a measure of conduction time from lower pons to midbrain. It is influenced by the impulses arising from the contralateral side. III -V IPL prolongation is considered abnormal only when it is associated with I - V IPL prolongation or abnormal V/I ratio.

I – V IPL:

It is a measure of nerve impulse conduction time from auditory nerve through pons and midbrain. Its upper limit is 4.5ms with inter aural difference is less than 0.5ms. It is prolonged in disorders like demyelination, degeneration, ischemia and tumors.

V/I Amplitude Ratio:

The absolute amplitudes don't have clinical utility as they are highly variable between individuals. To overcome this, the amplitude ratio V/I is used. As the wave I originated from peripheral portion of the auditory nerve and the wave V from the central portion of the CNS, their ratio helps to assess the synchrony of different parts of the auditory pathway. Its normal range is between 50% to 300%.

Non pathological factors affecting BAER: [60]

There are variety of factors which should be taken into account while performing and interpreting BAER. These factors are broadly classified into two categories,

- Subject factors
- Technical factors

Subject factors:

1.Maturation and Age:

Age is one of the most important factor while interpreting BAER waveforms. The first detectable component in preterm infant is wave I, which is seen in 30 weeks of gestation. Wave V is recorded in 33weeks of gestation. In normal term neonates the wave V is smaller than wave I. Amplitude ratio V/I is reversed compared to adults.[60] According to Stockard et al. the infants are having higher amplitude waves than in adults, presumably due to smaller head size and greater proximity of the recording electrodes to BAER generators. [69]

2.Gender Differences:

The absolute latencies and IPL are significantly shorter in females than in males by 0.1 to 0.2ms. [70] Absolute amplitude is greater in females. These differences are due to head size, greater

average brain size in males and higher core body temperature, shorter length of brainstem auditory pathway, faster maturation in females. [60, 63]

3.Body temperature:

For every one degree decrease in body temperature the latency of wave V increases about 0.15ms to 0.2msec. [60, 63] In hypothyroidism, the fall in the body temperature causes delay in nerve impulse conduction.

4.Subject Relaxation:

One of the most common difficulties in BAEP recording is myogenic response caused by excessive neck and facial muscle activity. This myogenic response is greater in post auricular muscle activity at the stimulated side and it can be reduced by placing the subject in supine position reduces the neck muscle tone thereby ensures muscle relaxation. If necessary , light sedation to induce sleep can be used, because anesthesia, sleep are not going to affect the BAER waveforms. [63]

5.Sleep:

No significant changes are detected in BAER parameters during natural sleep. But continuous monitoring reveals that minor fluctuation may be present in waves I & V which are related to nocturnal variations in body temperature not due to sleep stages. These fluctuations do not exceed 2%, so negligible. [63]

Technical Factors :

1.Stimulus intensity :

The resolution of waveforms are good and they are easily identifiable with the click intensities above 60dB HL(hearing level). Changes in the click intensities produce changes in the morphology of BAEP. When the click intensities decreases, the absolute latencies increases whereas the amplitude decreases. [63, 66]

2.Stimulus Polarity:

Rarefaction click polarity produce a larger wave I with a shorter latency and also it causes better separation of wave IV & V peaks than condensation clicks. To reduce the stimulus artifact, alternating polarity can be used. So alternating polarity is used in intra operative recording of BAER. [63]

3.Stimulus Frequency Spectrum:

In clinical neurophysiology laboratories unfiltered clicks with a broad frequency spectrum from 500 to 4000 Hz are used. For each specific stimulus frequency, specific regions of the basilar membrane in the cochlea is stimulated. At click intensities of 60 – 70dB HL, the 2000 to 4000Hz regions of cochlea is stimulated. [60, 63]

4.Stimulus Rate:

When the stimulus rate increases, it increases the absolute latency, IPL and decreases the amplitude of BAER waves. When the stimulation rate increased from 10 to 80 clicks / sec all BAER parameters increased. [60]

5.Filters :

The frequency spectrum used in BAER recording falls between 15 and 2000Hz and 50% of it falls in range below 200Hz. Therefore in clinical neurologic testing high pass filter is set at 10 to 30Hz and low pass filter is set at 2500 to 3000Hz. This gives better resolution of BAER waveforms. [60, 63]

BAER wave Abnormalities:

1. Absent wave I - tumor in peripheral portion of VIII cranial nerve.
2. Absence of waves from II, III:
    - acoustic neuroma
    - demyelinating disorder

BAER in Neurological Diseases:

- BAER waveforms are used to document the brainstem involvement in non-focal neurological diseases, especially those affecting the myelin.

- Prolongation of IPL I-III & I-V waves are reflecting the involvement of myelin which wraps the proximal and immediate intra axial portion of the cochlear nerve.
- BAER also helps to show the electrophysiological abnormalities even in clinically asymptomatic individuals.
- By latency intensity study, hearing threshold can be estimated and can be distinguished between conductive and SNHL.
- BAER waveforms are useful for the assessment of hearing in children and in patients who are unable to cooperate with conventional audiometry.

BAER in Hypothyroid Individuals

A study done at the Middlesex Hospital London on 1956, found that perceptive type of hearing loss is the most common type than conductive deafness in hypothyroidism. The investigators Howarth and Lloyd stressed that the perceptive deafness should not be overlooked because unlike other causes of sensorineural hearing loss, it shows considerable reversibility with treatment. [10]

Audiological study done by Bhatia et al in 1977 found that though conductive hearing loss seen in hypothyroidism patients sensorineural hearing loss is the most predominant type. [24]

Meyerhoff et al (1979) in their study to find the morphological, electrophysiological and biochemical reasons for hypothyroidism induced hearing loss, found that the cochlea is the site of lesion. [40]

Vant Hoff and Stuart in their study on deafness in myxedema observed that among 48 myxedema patients, 85% of them had sensorineural hearing loss. [22]

Parving et al 1983 in their study to find the hearing sensitivity in 15 myxedema patients, they demonstrated that all the hypothyroid patients had bilateral symmetrical SNHL. [23]

An evoked potential study done to assess the functional integrity of the brainstem auditory pathway in hypothyroid patients, Anjana et al found that there is slight increase in wave III latency but didn't find any significant difference in absolute and inter peak latencies in hypothyroid individuals. But they found significant improvement in latency of wave III and IPL I - III after thyroid hormone replacement therapy. By this study they proposed that there may be increased conduction time at the distal portion of the auditory pathway and the conduction velocity revert to normal with hormonal replacement. [16]

By recording BAER in 20 patients with hypothyroidism , Anand et al found the casual relationship between thyroid hormone deficiency and hearing loss and demonstrated the prolongation of absolute latency of wave I and IPL of I -III and I - V among 80% of their patients. They concluded that thyroid hormone deficiency causes retrocochlear lesions of the auditory pathway. [72]

Thornton and Jarvis, in their audiometric study on hypothyroid and hyperthyroid patients, found that in BAER , abnormal increase in the interpeak interval I-V and reduction in amplitude of waves III and V was found in hypothyroid patients whereas hyperthyroid patients didn't show any changes in the BAER waves compared to healthy controls. They reasoned that the abnormalities are due to low body temperature of the hypothyroid individuals. [73]

In a follow up study done, Hohmann et al found that hypothyroidism causes prolongation of BAER latencies I – V . After the treatment with thyroxine hormone for six months the hypothyroid patients showed improvement in the latencies. [74]

Mahin et al found that prolongation of BAER in congenital hypothyroid patients[75]. Chou et al and Bellman et al by using BAER identified the persistence of neuro otological dysfunction even after starting of treatment of congenital hypothyroidism.[76]

Khechinaschvili et al in their study on the hearing system under thyroid hypo function investigated 50 hypothyroid patients. By using BAER they detected 30% of the SNHL cases. In their study they observed that treatment with thyroxine hardly improves the hearing disorders.[77]

Di Lorenzo et al recorded the BAER with masking wide band in 56 adult hypo and hyperthyroid patients, found that there is a relationship between BAER alterations and the degree of thyroid dysfunction.[78]

Huang and coworkers in National Taiwan university who have done a evoked potential study in thyroid disease patients reported that significant prolongation of waveform latencies and interpeak latency of BAER seen in hypothyroid patients than the hyperthyroid patients. Thus they concluded that central nervous system is more sensitive to hypothyroidism than hyperthyroidism.[79]

Himelfarb et al in their study on Auditory brainstem responses in patients with thyroid dysfunction inferred that the characteristic changes in the BAER were prolonged brainstem conduction time, flattened peaks and diminished amplitude. He added that these changes correlated well with serum levels of T_4. [80]

On the experimental level, Lai et al demonstrated an early increased BAER IPL I -V and III - V in the experimentally induced hypothyroid rats and concluded that CNS is highly vulnerable to thyroid hormone deficiency. [81]

Moore et al observed that, the acoustic motor reflex and BAER require synchronized neural pathway activation. For that there will be tight regulation of myelination must be needed. Thyroid hormone regulates the neuronal myelination process. [54]

Rubenstein et al[82] in guinea pigs and Ben Tovim et al[83] in rats, both of them induced hypothyroidism experimentally in those animals and recorded BAER. From their study they demonstrated the prolongation of all the absolute latencies and interpeak latencies and also found that the prolongation of BAER latencies directly associated with fall in the serum levels of free thyroid hormones.

From all these evidences it is clear that hypothyroidism affects the central auditory pathway, evoked potentials like Brain stem Auditory Evoked Response is helpful to identify the auditory system involvement . So in the current study we sought to study the absolute latencies and inter peak latencies of brainstem auditory evoked responses in newly diagnosed hypothyroid individuals.

MATERIALS & METHODS

MATERIALS AND METHODOLOGY

STUDY DESIGN:

This is a Cross Sectional study.

STUDY PLACE:

This study was performed in the Research laboratory of Department of Physiology, Coimbatore Medical College, Coimbatore.

STUDY PERIOD:

The study period extended from August 2013 to June 2014.

The ethical committee of the Coimbatore Medical College approval was obtained prior to the commencement of the study.

INCLUSION CRITERIA:

A total of 80 subjects of 20 - 50 years were included in the study. All participants were females. Among them forty were newly diagnosed hypothyroidism patients and forty were normal healthy females.

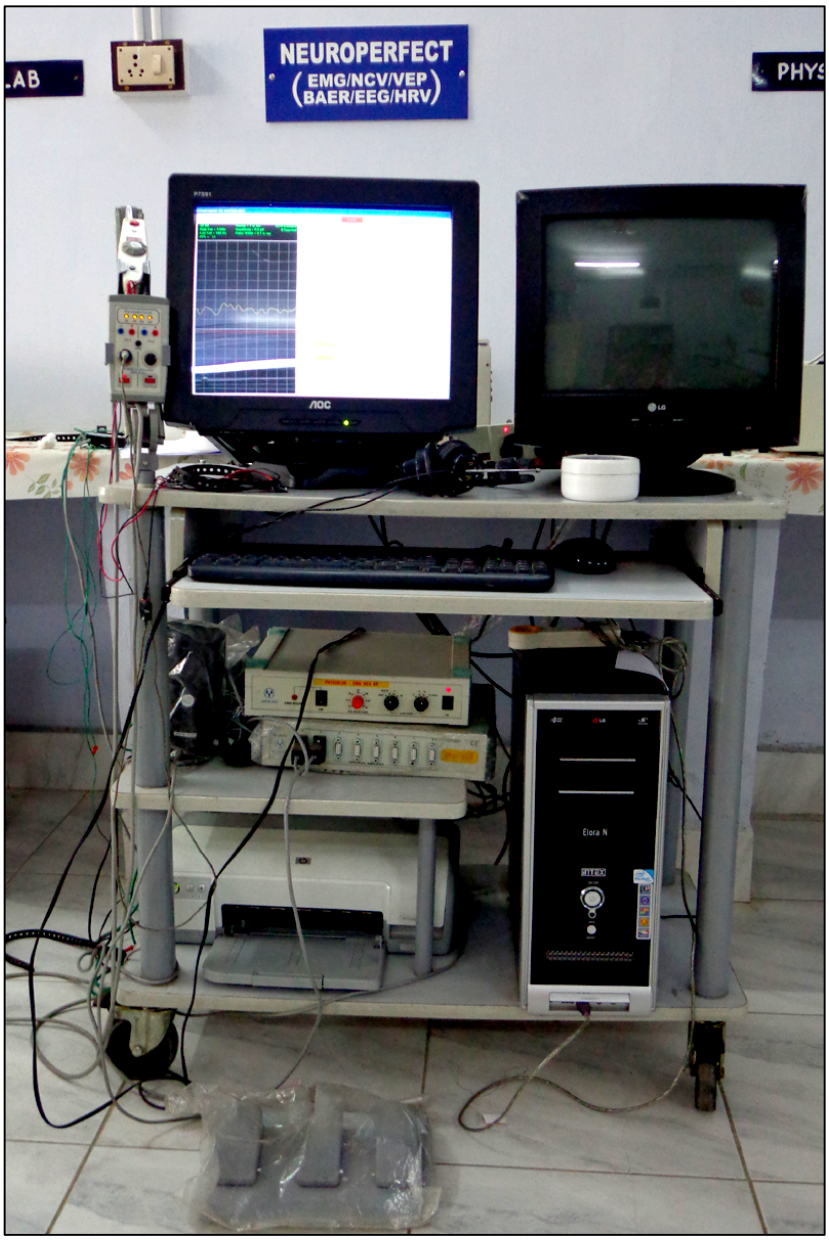
EXCLUSION CRITERIA:

- Known patients of hypothyroidism already on treatment,
- Persons working in noisy environment
- Pregnant females,
- Known cases of any hearing loss,
- Systemic illness like diabetes mellitus, hypertension, collagen disorders and neurodegenerative diseases
- H/o drug intake - ototoxic drugs, anticonvulsant drugs, antimalignant drugs.
- H/o head injury
- H/o prior ear surgery were excluded from the study.

CASE SELECTION:

Patients who came with the symptoms and signs suggestive of hypothyroidism such as easy fatiguability, dry skin, hoarseness of voice, cold intolerance, weight gain, periorbital swelling and bradycardia were randomly selected from the medicine outpatient department. Thyroid profile was done for all of them which include the serum parameters of TSH, free T_3, free T_4. 40 patients diagnosed

NEUROPERFECT



as hypothyroidism were selected as study subjects and 40 age matched healthy females with normal thyroid profile were taken as controls. They were selected from the general population in Coimbatore. None of the cases and controls had any symptoms and signs of CNS dysfunction and none of them showed any abnormality in neurologic examination and were not on treatment with thyroxine.

MATERIALS USED FOR THE STUDY:

- Proforma - To obtain detailed history and to record the clinical examination findings.
- Portable weighing machine – to record the body weight in kilograms.
- Stadiometer – to measure the standing height in centimeters.
- ERBA thyro kit – To measure the serum levels of TSH, free T3 and free T4 .
- Neuroperfect EMG 2000 system with installed BAER software to record absolute latencies and interpeak latencies.

METHODOLOGY :

The institutional ethical committee approval was obtained prior to the commencement of the study and the subjects were selected and grouped. The study was carried out after explaining the procedure in detail and getting informed written consent from both the cases and controls. BAER recorded between 10 A.M to 2 P.M. All the techniques of measurement were maintained uniformly throughout the study.

The study protocol involved,

1. Detailed history was elicited from them to diagnose the hypothyroidism and to rule out the prior neurological and endocrine disorders.

2. **Measurement of anthropometric indices**

Weight of subject: The subjects were asked to stand erect with their arms relaxed at their side, with both feet close together. By using a portable standard weighing machine, weight in kilograms was recorded .

COLLECTION OF BLOOD SAMPLE

ELISA READER

Height of subject: By using a stadiometer , height of subject in centimetres was measured by asking the subject to stand erect and the vertical height was measured.

BMI of subject: Body Mass Index was calculated using the Quetelet's index. BMI = Weight (Kg) / Height^2 (m)

3. A thorough clinical examination of the study subjects were done. It consists of general examination, systemic examination which includes respiratory system, cardiovascular system, abdomen and central nervous system. Otorhinolaryngological examination was done for the presence of cerumen in ear, abnormality in external auditory canal, otorrhea, and foreign body in the ear.

4. All participants underwent thyroid profile measurement.

Hormone measurement:

Thyroid profile includes serum TSH, free T_4, free T_3 and they measured by microplate based Enzyme Linked Immuno Sorbent Assay (ELISA) using ERBA kit. This method is based on one step immune enzymatic principle associated with the Biotin – Streptavidin Technology.

RINNE'S TEST

The reference values are,

- TSH – 0.4 to 5.5 μIU/ml
- freeT3 – 1.4 to 4.2 pg/ml
- freeT4 – 0.8 to 4.2 ng/ml

5. **Rinne's test** was done in all participants to compare air conduction with the bone conduction of each ear separately. It is done by placing the base of the vibrating tuning fork of 512Hz over the mastoid process and the subject is asked to raise the hand when she stops hearing the sound. Then immediately transfer the tuning fork which is still vibrating to the side of the head and is held in front of the ear.

If the hearing is normal, the subject can hear even after he has stopped hearing the vibrations by bone conduction. It implies that air conduction is better than bone conduction. It is referred as Rinne's positive. If there is CHL, vibrations are not heard after bone conduction is over. It is referred as Rinne's negative.

Weber's test was done in all subjects to study bone conduction. The base of the vibrating tuning fork of 512Hz kept either in the middle of the forehead or on the vertex and the

WEBER'S TEST

subject was asked to indicate in which ear the sound is heard better or heard equally in both ears. This is expressed as lateralization of sound to a particular ear.

Healthy individuals heard the vibrations equally in both the ears. In individuals with CHL, the sound is heard better by the defective ear. In individuals with SNHL, the sound is better heard by the normal ear.

Procedure for recording Brainstem Auditory Evoked Potentials:

The BAER was recorded by using Neuroperfect EMG 2000 system with installed BAER software. The subjects were asked to sit comfortably in fully relaxed state and with eyes closed. The skin at the site of placement of surface electrode was cleaned with spirit and the electrodes were placed on the scalp, according to the 10 - 20 International System using EEG paste.

The site of placement of electrodes:

- Active electrode on the Verterx (Cz)
- Reference electrodes over the Right and Left mastoid process
- Ground electrode on the forearm

BAER RECORDING IN PROGRESS

All the above sites the skin to electrode contact impedance was kept below 5 Kohms. Each ear was tested separately. The acoustic stimuli was given in the form of monaural click stimuli by using head phones. In this study rarefaction type of stimuli is used, because it will produce better resolution of the BAER waves. The filter frequency was set between 100 to 3000 Hz, analysis time 10ms and sensitivity 1μV/division. A total of 2000 stimuli at the frequency of 10Hz were delivered to the testing ear within 0.1ms. The intensity of stimulus was 60dB above the sound pressure level. To the contralateral ear 40dB white noise was given for masking. Two or three trials were performed in order to demonstrate the consistency of the wave form. The absolute latencies of all BAER waves and their IPL of I-III, III-V and I-V were marked with the help of digital cursors and the values were noted down.

BAER RECORDING IN CONTROLS

DEPARTMENT OF PHYSIOLOGY

COIMBATORE MEDICAL COLLEGE
COIMBATORE
Phone Number :

 # JESY28 **sumathy**

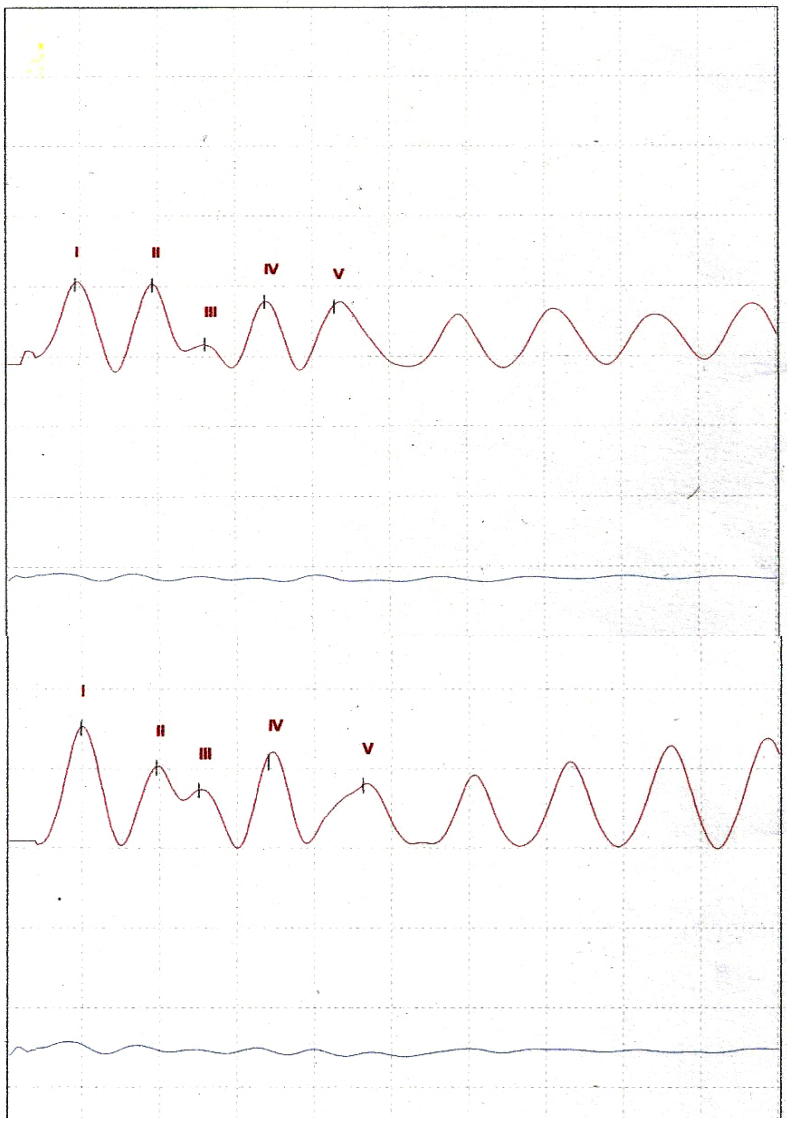
Sensitivity	Frequency	Duration	Sweep	Intensity
3 µV	100 Hz-3 KHz	0.1 m sec	1 m sec	60 dB

Medicaid

BAER 2/14/2014

Right Ear

Left Ear



BAER RECORDING IN CASES

DEPARTMENT OF PHYSIOLOGY

COIMBATORE MEDICAL COLLEGE
COIMBATORE
Phone Number :

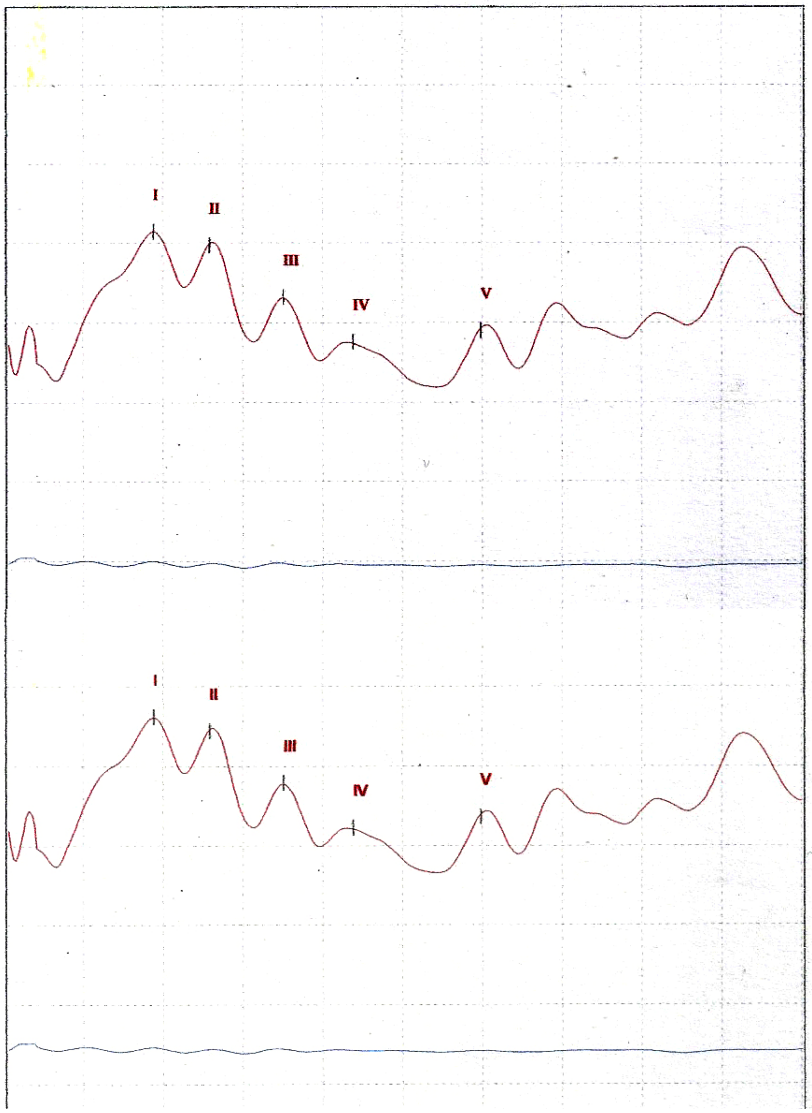
 # JESY17 padmavathi

Sensitivity	Frequency	Duration	Sweep	Intensity
1 µV	100 Hz-3 KHz	0.1 m sec	1 m sec	60 dB

Medicaid

BAER 2/6/2014

Right Ear



Left Ear

STATISTICAL ANALYSIS

STATISTICAL ANALYSIS

The data collected from the selected subjects were recorded in a Master Chart. The mean values of both ears were calculated and analyzed with the help of **Epidemiological Information Package (EPI 2010)** which developed by Centre for Disease Control, Atlanta.

Using this software mean, standard deviations and 'p' values were calculated. **Unpaired 't' test** was used to compare BAER latencies and interpeak latencies of newly diagnosed hypothyroid patients and healthy controls. **Pearson's correlation coefficient** was calculated using Excel software. 'p' value less than 0.05 was considered to denote significant relationship.

Microsoft word & excel were used to create the tables, charts and graphs.

RESULTS

RESULTS

The present study was carried out in the Research laboratory, Department of Physiology, Coimbatore Medical College, Coimbatore. The absolute and interpeak latencies of BAER were recorded by using Neuroperfect EMG 2000 system with installed BAER software.

1. Study population

A total of 80 females were included in the study. Among them 40 females were newly diagnosed hypothyroid patients and 40 females were normal healthy controls. They divided into two groups:

Group A – Newly diagnosed Hypothyroid individuals

Group B – Normal Healthy females

The mean age was 37.05 years for newly diagnosed hypothyroid females and 36.02 years for normal healthy females. There were no significant difference between the groups so they were comparable. The mean Body Mass Index of the Group A was 25.3 kg and Group B was 23.1 kg. The hypothyroid patients had higher BMI than control group.

Table -1: Demographic characteristics of Study Population

Variables	Group A	Group B	'p' value
Participants	N=40	N=40	
Mean age (years)	37.05	36.02	0.3028*
Mean Height(cm)	153.7	155.2	0.1825*
Mean Weight(kg)	59.7	55.7	0.0011**
Mean BMI	25.3	23.1	<0.0001**

*** - Non Significant, ** - Significant**

Figure -1: Height / Weight / BMI

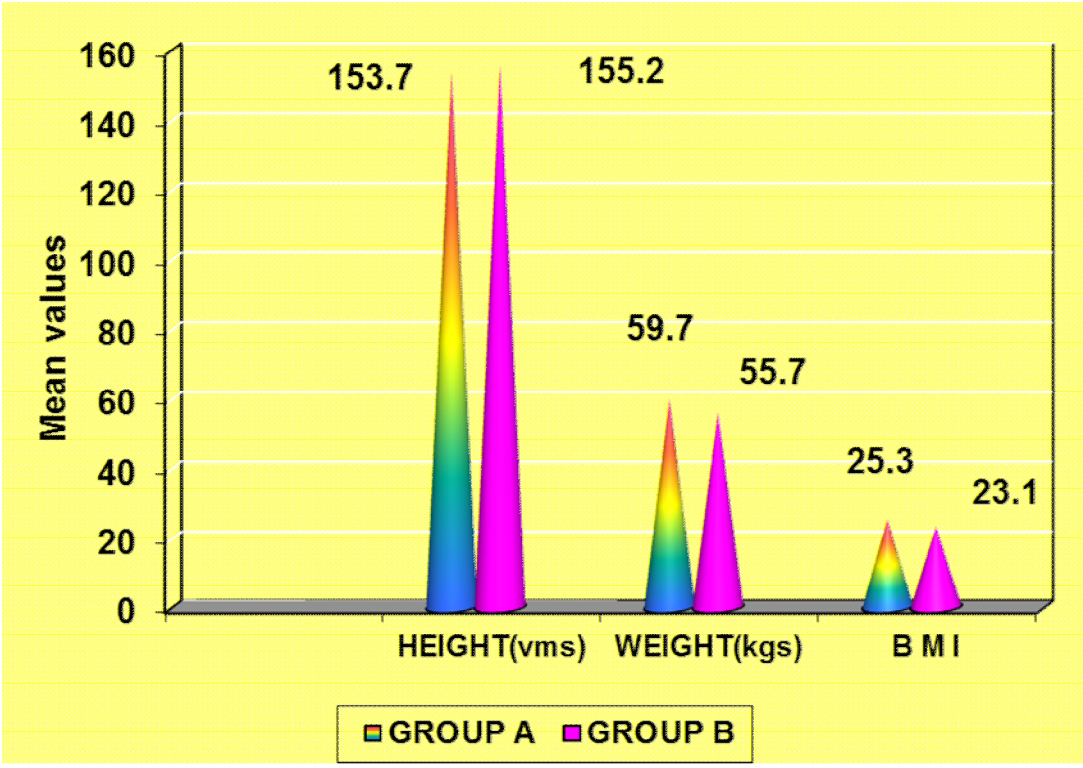


Table 2 : Age Distribution

Age Group (in years)	Group A		Group B	
	No	%	No	%
20 – 30	9	22.5	13	32.5
31 – 40	15	37.5	14	35.0
41 – 50	16	40	13	32.5
Total	40	100	40	100

About 77.5% of the newly diagnosed hypothyroid females were predominantly in the age group of 31 to 50 years

Figure -2: Age distribution

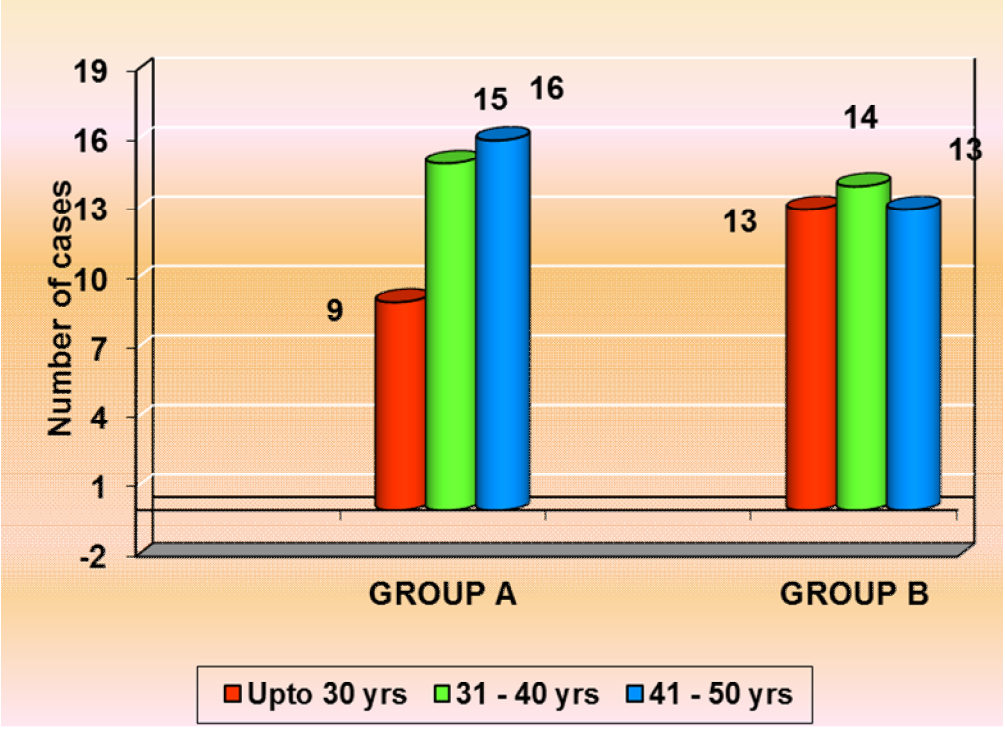
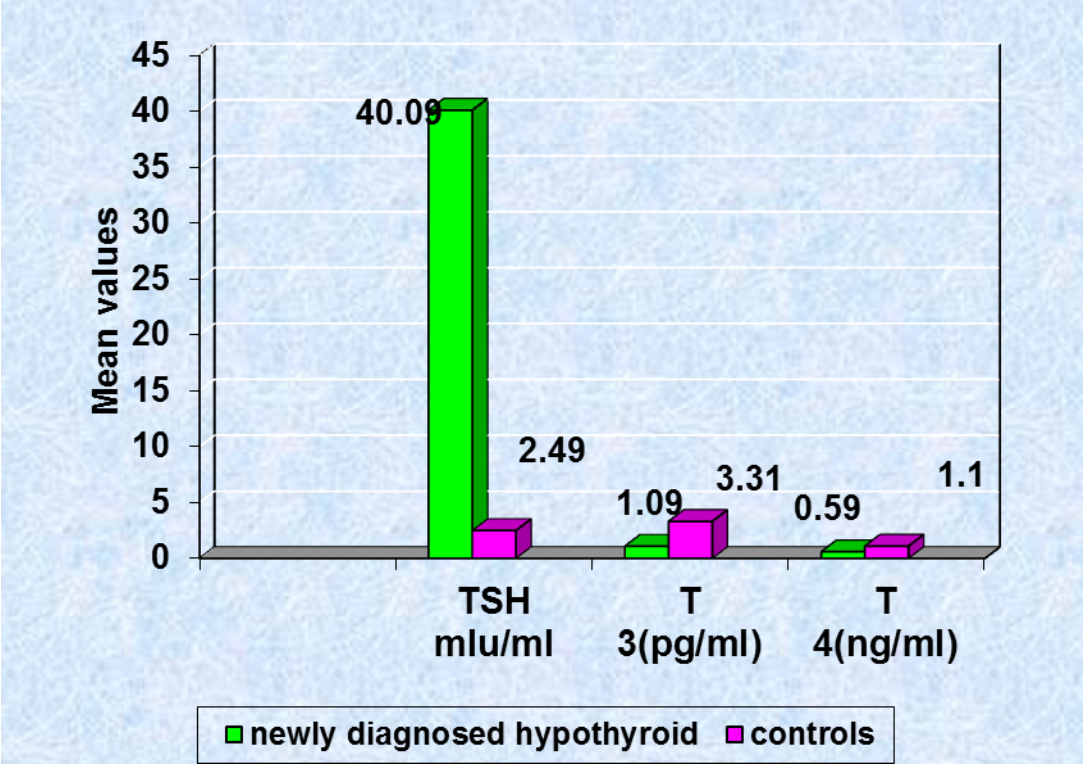


Table 3 : TSH (mIU/ml)/ T3 (pg/ml) / T4 (ng/ml)

Thyroid profile	Group A		Group B		'P'
	Mean	SD	Mean	SD	
TSH(mIU/ml)	40.09	4.05	2.49	1.27	**<0.0001 Significant**
T3 (pg/ml)	1.09	0.56	3.31	0.7	**<0.0001 Significant**
T4 (ng/ml)	0.59	0.28	1.1	0.28	**<0.0001 Significant**

There was significant difference in thyroid profile between study and control group. Hence the groups were comparable.

Figure -3: Thyroid Profile of newly diagnosed hypothyroid patients and controls.



BAER Recordings

Among the Seven Waveforms of BAER, I, III, V waves are constant , clinically useful and reproducible. The absolute latencies I, III, V and IPL I-III, III-V, I-V were recorded from both ears. The mean values were tabulated in table 4 and 5.

Table 4 : Latencies in newly diagnosed in Hypothyroid patients and controls

Latencies	Group A		Group B		'p' Value
	Mean	S.D	Mean	S.D	
Right ear					
I	2.04	0.41	1.51	0.37	**<0.0001 Significant**
III	4.85	0.75	3.78	0.72	**<0.0001 Significant**
V	7.78	0.96	5.68	0.89	**<0.0001 Significant**
Left ear					
I	2.03	0.37	1.54	0.39	**<0.0001 Significant**
III	4.86	0.81	3.74	0.73	**<0.0001 Significant**
V	7.97	0.73	5.66	0.96	**<0.0001 Significant**

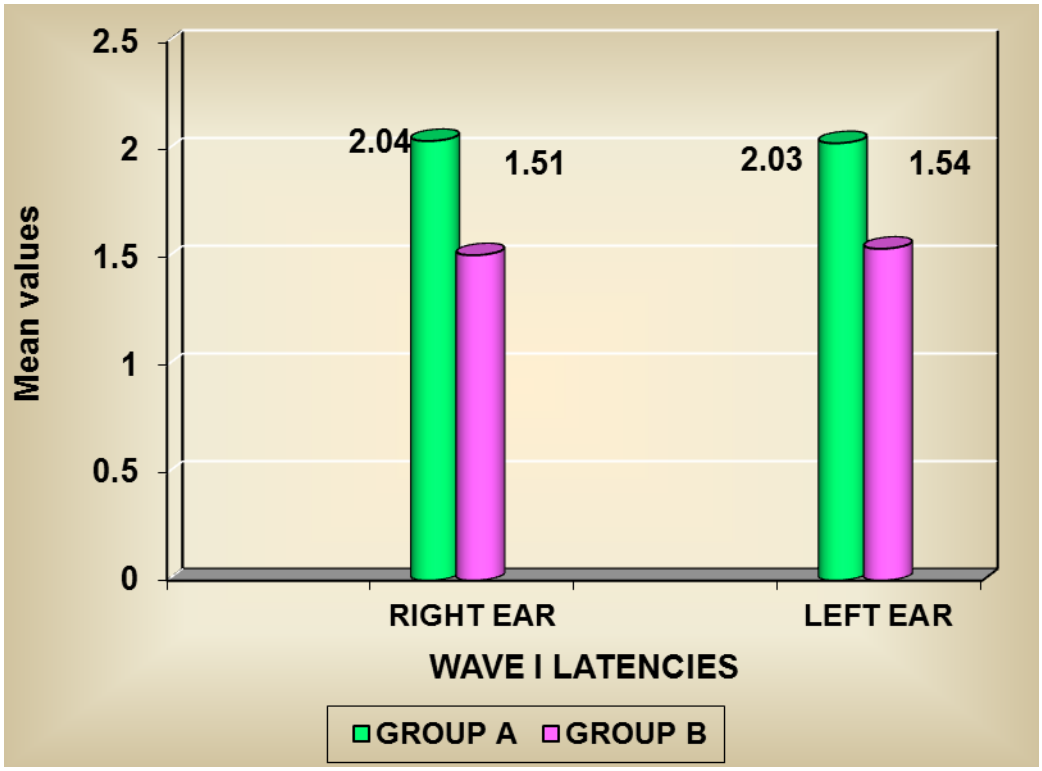
Table 5 : Interpeak Latencies in in newly diagnosed in Hypothyroid patients and controls

Interpeak Latencies	Group A		Group B		'p' Value
	Mean	SD	Mean	SD	
Right ear					
I – III	2.94	0.45	2.34	0.43	**<0.0001 Significant**
III – V	2.57	0.39	2.06	0.4	**<0.0001 Significant**
I – V	5.67	0.60	4.33	0.63	**<0.0001 Significant**
Left ear					
I – III	2.9	0.42	2.21	0.41	**<0.0001 Significant**
III – V	2.63	0.34	1.97	0.41	**<0.0001 Significant**
I - V	5.65	0.68	4.32	0.55	**<0.0001 Significant**

1. Wave –I latency

The mean Absolute latencies of BAER waveform in newly diagnosed hypothyroid females were 2.04±0.41, 2.03±0.37 and in healthy females were 1.51±0.37, 1.54±0.39 for both right and left ears respectively. The latencies were significantly prolonged ($p < 0.0001$) in newly diagnosed hypothyroid females when compared to healthy females. The comparison of wave I latencies between newly diagnosed hypothyroid females and healthy females is shown in figure 4.

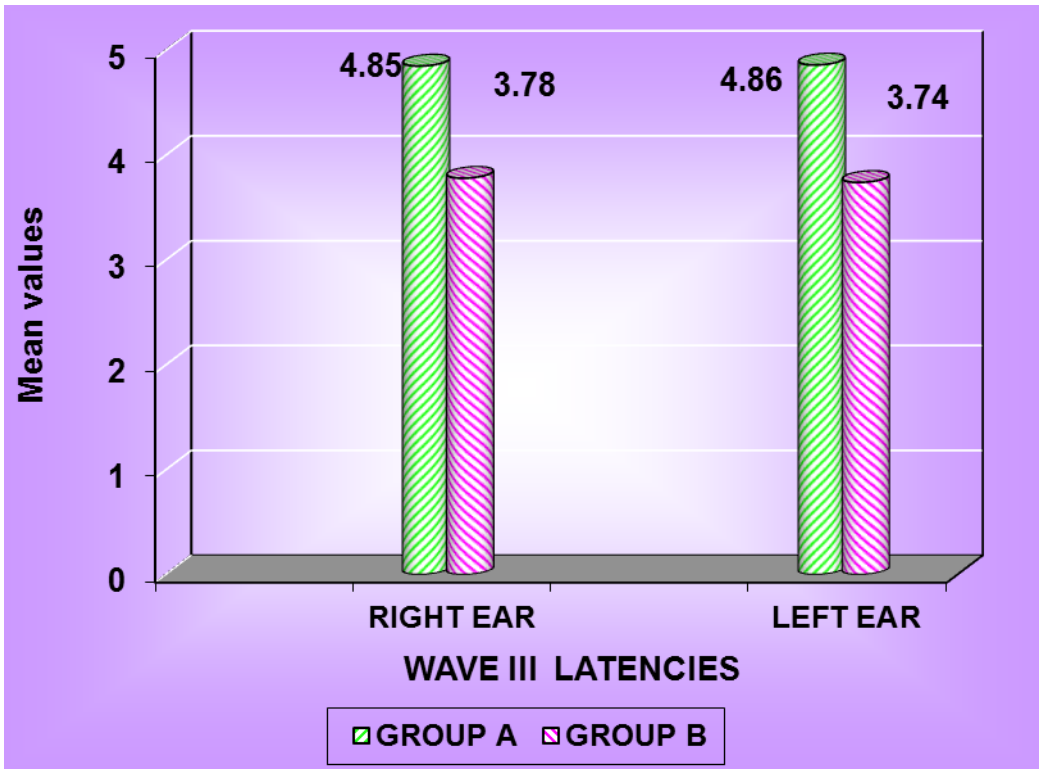
Figure -4: Wave I latency



2. Wave III latency

The mean absolute latencies in newly diagnosed hypothyroid females was 4.85±0.75 and 4.86±0.81 and in healthy females was 3.78±0.72 and 3.74±0.73 for both right and left ears respectively. A significant prolongation was seen in hypothyroid individuals. P value for both ears were <0.0001. (figure 5)

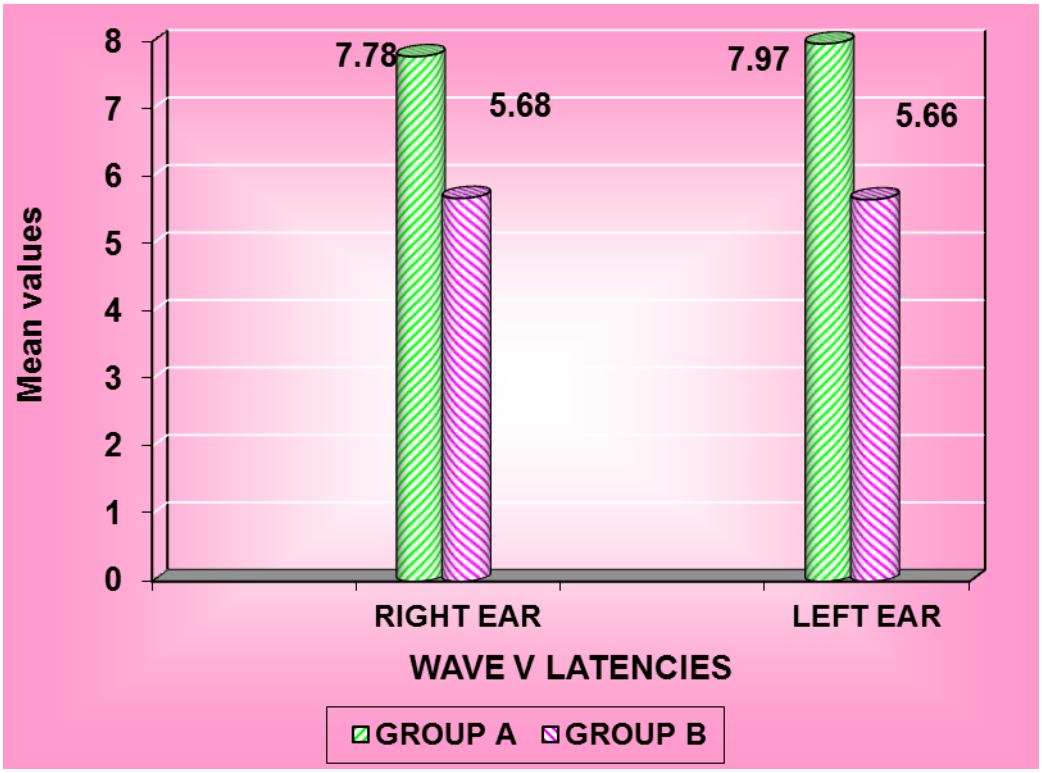
Figure -5: Wave III latency



3. Wave V latency

The mean and standard deviation of wave V among newly diagnosed hypothyroid females and healthy females are as follows: Newly diagnosed hypothyroid females group had 7.78±0.96 and 7.97±0.73 for right and left ear respectively. Healthy females had 5.68±0.89 and 5.66±0.96 while recording in right and left ear respectively. Newly diagnosed hypothyroid females have a significant increase in wave V latencies when compared with healthy females (P value <0.0001 for both ears).

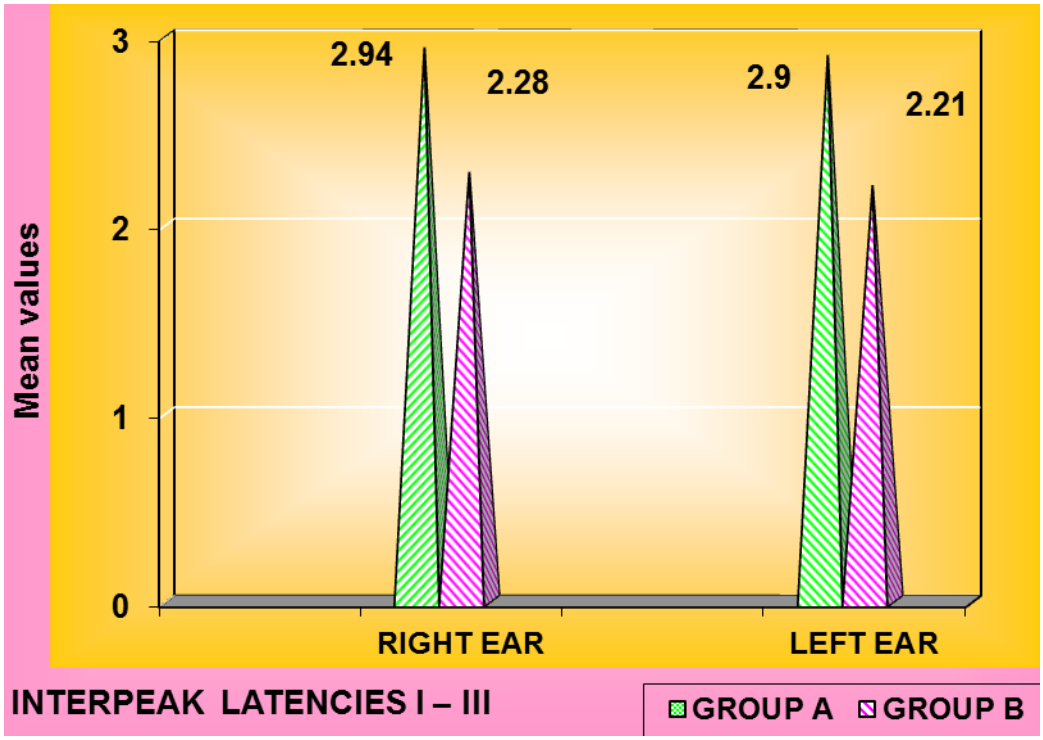
Figure -6: Wave V latency



4. Interpeak latency I-III

The mean Interpeak latency I-III in newly diagnosed hypothyroid females was 2.94±0.42 and 2.9±0.42 and in healthy females was 2.28±0.43 and 2.21±0.41 for right and left ear respectively. Comparing the mean interpeak latency of I-III between in newly diagnosed hypothyroid females and healthy females showed a significant prolongation of Interpeak latency among newly diagnosed hypothyroid females (P value <0.0001 for both ears).

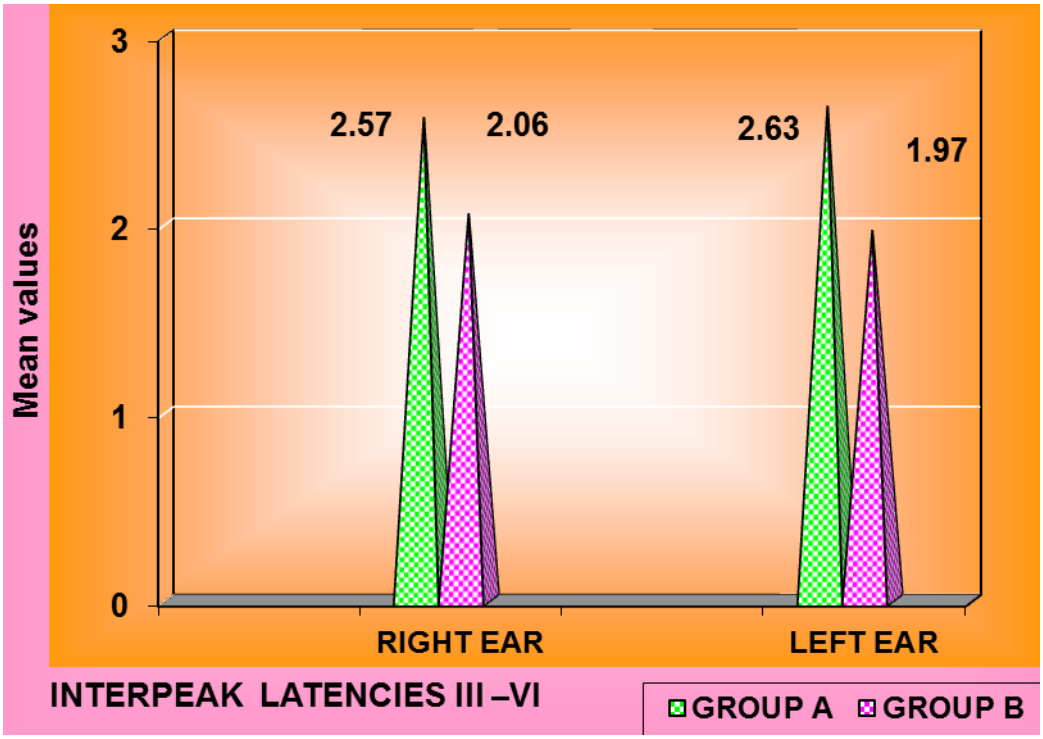
Figure – 7 : Interpeak latency I – III



5. Inter peak latency III-V

The overall mean Interpeak latencies of BAER waveform in newly diagnosed hypothyroid females was 2.57±0.39 and 2.63±0.34 and in control group was 2.06±0.40 and 1.97±0.41 for right and left ears respectively. There was significant difference between the two groups (P value<0.0001 for both right and left ears). The results are depicted in figure. 8.

Figure – 8: Interpeak Latency III - V



6. Inter peak latency I-V

The mean and standard deviation for Interpeak latencies I-V among newly diagnosed hypothyroid females and healthy females are as follows. The I – V Interpeak latency of Newly diagnosed hypothyroid females have of 5.67±0.60 and 5.65±0.68 for right & left ear respectively. In Healthy females the I – V Interpeak latency was 4.33±0.63 and 4.32±0.55 while recording in right and left ear respectively. The comparison between the two groups revealed significant ' p' value of <0.0001 in both ears.

Figure 9: interpeak latency I- V

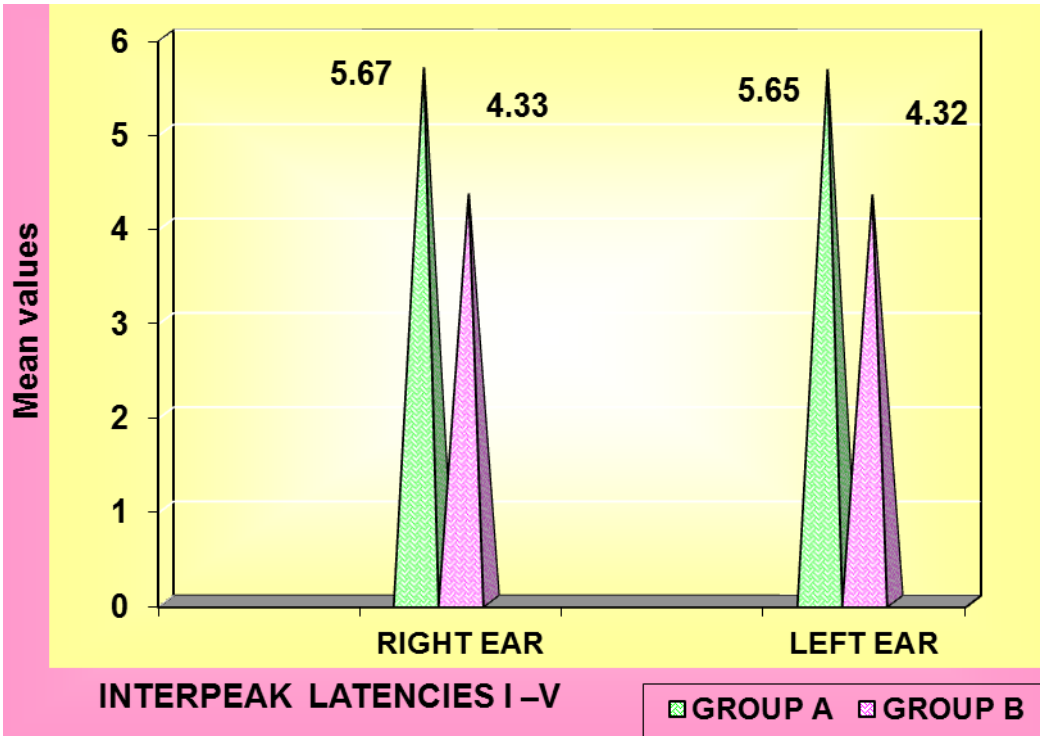


Table 6 : interaural differences of Latencies and interpeak latencies in newly diagnosed in Hypothyroid patients

There is no statistically significant interaural differences of absolute latencies and interpeak latencies in newly diagnosed hypothyroid patients.

WAVES	Right Ear		Left Ear		'P'
	Mean	SD	Mean	SD	
I	2.04	0.41	2.03	0.37	= 0.9091 Not Significant
III	4.85	0.75	4.86	0.81	= 0.9545 Not Significant
V	7.78	0.96	7.97	0.73	= 0.3221 Not Significant
I – III	2.94	0.42	2.9	0.42	= 0.6713 Not Significant
III – V	2.57	0.39	2.63	0.34	= 0.4655 Not Significant
I - V	5.67	0.60	5.65	0.68	= 0.8894 Not Significant

Table 7: Correlation between TSH, T3 & T4 and latencies and interpeak Latencies

There was positive correlation between serum TSH and the BAER parameters and a negative correlation was found with serum free T_3, free T_4.

Correlation with	Correlation coefficient (r) of		
	TSH	T_3	T_4
Right ear Latencies			
I	0.6085	-0.5265	-0.562
III	0.5421	-0.3841	-0.4496
V	0.3826	-0.3145	-0.299
Left ear Latencies			
I	0.5681	-0.3881	-0.4654
III	0.4703	-0.2562	-0.304
V	0.2474	-0.0919	-0.1615
Right ear inter peak Latencies			
I – III	0.3186	-0.2506	-0.2383
III – V	0.1148	-0.0367	-0.0306
I - V	0.2441	-0.1579	-0.2662
Left ear interPeak Latencies			
I – III	0.3398	-0.1441	-0.2374
III – V	0.0726	-0.1237	-0.0237
I - V	0.2666	-0.1226	-0.2705

DISCUSSION

DISCUSSION

Among the thyroid disorders Hypothyroidism is one of the most common thyroid dysfunction. Central nervous system dysfunctions are the important consequences of hypothyroidism. It is associated with motor deficits, hearing impairment, mental retardation, depression and memory deficit. The most common otolaryngological manifestation of hypothyroidism is hearing impairment.[11] It may be conductive, sensorineural or mixed type of hearing loss. Parving et al[23] in 1983 and Isam et al in 2001[24] were reported in their study that SNHL was the predominant type of hearing loss in hypothyroid people. Early treatment of hypothyroidism with thyroid hormone will completely revert the hearing impairment.[12]

Intact anatomical pathway, relay stations and proper myelination of nerves are some of the factors that determine the functional ability of the auditory pathway.[16] The absolute and inter peak latencies in BAER recordings denote the conduction of nerve impulses along the different segments of the auditory pathway and it also can be used as a tool to assess the hearing impairment.

The present study deals with the BAER changes in newly diagnosed hypothyroid individuals. The Absolute and interpeak latencies were recorded and analyzed between newly diagnosed hypothyroid individuals and healthy controls. In this study all participants were females. There are many studies which documented the gender differences on BAER recordings.[70,84,85] So in the present study only the hypothyroid females were selected to get more definite results. They were subjected to the same procedures, technical and environmental conditions.

Various electrophysiological studies provide an almost unanimous opinion that thyroid hormone substitution promotes complete reversal of hearing loss.[11,13,15-17] Therefore to make sure that the changes in the BAER parameters are exclusively due to thyroid hormone deficiency, only the newly diagnosed hypothyroid females were selected in this study.

In the present study 40 newly diagnosed hypothyroid females of mean age 37.05 years and normal healthy females of mean age 36.02 years were included. About 77.5% of the newly diagnosed hypothyroid females were predominantly in the age group of 31 to 50 years. It is consistent with the report of myxedema committee in London which said that middle aged women were mostly affected by hypothyroidism than men.[45]

The BAER are far field subcortical electrical potentials which helps to assess the auditory sensory process from distal part of the cochlear nerve to the brainstem.[56,60] So in this study the BAER was recorded among newly diagnosed Hypothyroid females and healthy females and found that there was statistically significant ($p<0.0001$) increase in absolute latencies of wave I, III and V in newly diagnosed hypothyroid females. Similarly interpeak latencies I - III, III-V and I-V were also prolonged significantly ($p < 0.0001$) in them compared to controls . This was consistent with the study results of other researchers.[11,72,78,79.]

A study done to investigate the neurophysiological effects of thyroid hormone by Huang et al observed that of BAER seen in hypothyroid patients and concluded that central nervous system is more sensitive to thyroid hormone deficiency.[79]

In 1981 Himelfarb et al in their study on Auditory brainstem responses in thyroid disorders inferred that the changes in the BAER pattern was characterized by prolonged brainstem conduction time, flattened peaks and diminished amplitude.[80]

CL Lai from Taiwan analyzed the brainstem auditory evoked responses from 20 patients of primary hypothyroidism , observed that the peak and interpeak latencies were delayed significantly in them. [87]

Anjana et al in their evoked potential study found a delayed conduction of impulses along the superior olivary nucleus which leads an increased wave III latency but did not find any significant difference in other absolute and IPL of hypothyroid individuals. They found significant improvement in wave III conduction time and IPL of I -III after thyroid hormone therapy. By this study they proposed that optimal thyroid hormone level is required to improve the excitability of neuronal generators in the brainstem auditory pathway particularly for wave III and V. [16]

Another study done by Santos et al to find the audiological parameters in the patients of acute hypothyroidism concluded that cochleovestibular symptoms like hearing loss and vertigo were more frequent in them. In addition to it there were altered BAER values with higher latencies of waves I , III and V especially absolute latency of wave V showed statistically significant prolongation ($P < 0.05$) and considered that this delay was attributed to the lesion at the level of endocochlear, retrocochlear and central structures of the auditory pathway.[11]

Khedr et al did a study in hypothyroid patients and found a significant prolongation of all wave latencies and inter peak intervals of BAER. By their study they suggests that hypothyroidism affects the nervous system in a diffuse manner. All these findings go in favor of the present study results. [9]

The BAER waveform I arises from the peripheral part of the cochlear nerve. The wave III originates from superior olivary nucleus in pons whereas wave V arises from inferior colliculus of midbrain.[56,60] In our study there was a significant increase in the absolute latencies of wave forms I, III, V was observed. Similar to the present study results, Thornton and Jarvis from MRC institute of hearing research, UK, [73] Santos et al,[11] Khedr et al [9] and Hohman et al[74] were also showed increase in the wave latencies. They suggested that this may be due to slow conduction of nerve impulses along the auditory pathway. Because the BAER wave latencies depends on the functional integrity and myelination of the auditory pathway. [16]

Hypothyroidism being a metabolic disorder it affects the oxidative activity of mitochondria, lipid level in the CNS, protein synthesis and degradation which leads to demyelination .[11] The increased absolute latency of I, III and V in this study

indicates that the thyroid hormone deficiency affects the myelination of both peripheral and central part of the auditory pathway. It was further supported by the molecular level experimental studies.

Moore et al and Knipper et al inferred that thyroid hormone is essential for the expression of myelin genes like peripheral protein zero(P0), major basic protein(MBP) and proteo lipoid protein(PLP) in cochlea, brainstem and auditory cortex. So thyroid hormone deficiency will lead to hypomyelination of the peripheral and central part of the intradural segment of the auditory nerve and produces enhanced wave latencies. [41, 54, 88]

In 1983 Abbott et al said that the prolonged central conduction time of nerve impulse in hypothyroidism may be attributed to low body temperature and altered cerebral metabolism.[55]

Regarding Inter peak latencies of BAER, the IPL I-III measures the neuronal conduction along the VIII nerve across the subarachnoid space into lower pons, whereas III - V denotes the conduction time from lower pons to midbrain . The IPL I-V measures of neuronal conduction time from the VIII nerve through pons and midbrain. Thus the inter peak latencies gives information about the functional integrity of the mid portion of the brainstem auditory pathway.[56, 60, 63]

In the present study there was a significant prolongation of all IPL observed in newly diagnosed hypothyroid patients. This result was consistent with the results of Anand et al[72], Di Lorenzo et al[78], Santos et al[11] and Khedr et al[9].

A prospective cohort study done by Chandrasekhar et al[17] and another cross sectional study done by Gowri V [89] discovered a significant delay in latencies of the wave forms III , V and IPL I-V in acquired hypothyroid patients without treatment. They explained that the significant prolongation may be attributed to hypothermia, altered metabolism of brain and dysfunctional regulatory proteins like otoferlin, prestin which are necessary for the auditory sensation .

Many experimental studies have been done at molecular level to elucidate the relationship between thyroid hormone and the auditory function. One such experimental study done on 26 adult myxedematous albino rats showed the reversible dynamic changes in the amplitude of wave III of BAER and concluded that the lesion was mainly in the superior olivary nucleus in the brainstem. [82]

Saito et al, in their study on hypothyroid dogs, found structural changes in the membranous labyrinth and in the petrous part of the temporal bone and also demonstrated the neuronal cell reduction in the cerebral cortex. [90]

Knipper et al done an experimental study on wister rats, recorded Auditory brainstem response and Distortion product otoacoustic emission(DPOAE) in methimazole (MMI) treated adult rats and found that DPOAE was absent and Auditory brainstem response latencies were prolonged when compared with controls. They found that the prolongation of auditory brainstem responses as a result of thyroxine deficiency before the onset of hearing are permanent and also added that thyroxine is essential for the neuronal and structural development of the inner ear, as well as for the auditory function. So its deficiency affects the auditory system from the periphery to central aspect of the auditory pathway in a centripetal fashion. The BAER provide the information about the maturation of central auditory process which includes myelinogenesis, maturation of synapses and dendrites. [88]

Apart from the above electrophysiological, experimental studies, biochemical and basic histological studies may also explain the association between the auditory dysfunction and thyroid

hormone deficiency. By using immunohistochemistry stains , researchers found the presence of thyroid receptors in the spiral ganglion and inner hair cells of the rat cochlea. Hypothyroidism which affects all the metabolic functions of human body leads to energy deficit. This leads to reduced oxidation and causes deposition of glycogen along the nerves which results in axonal degeneration, segmental demyelination. This constitutes the possible basic pathogenic mechanism of nervous dysfunction in hypothyroidism.[91]

Bell et al added that decreased absorption of calcium also contributes to the delayed synaptic transmission along the auditory pathway. [17] Deficiency of thyroid hormone down regulates the voltage gated sodium current density and leads to reduced firing frequency and delayed action potential upstrokes in turn reduces the conduction velocity. [92]

The overall findings signify that both peripheral and central auditory pathway affected by hypothyroidism. The proposed possible mechanisms for the hearing loss in hypothyroidism are multifactorial, like defective myelination, reduced body temperature, altered cerebral metabolism, diminished regulatory protein actions, reduced sensitivity of sensory receptors, decreased voltage gated sodium current density and axonal degeneration caused by deposition of glycosaminoglycan.

In contrary to the above studies, some of the researchers have showed disagreeing results in their studies. A study by Vanasse et al done on 15 adult hypothyroid patients of age ranging from 34 to 82 years found no significant differences in BAER before treatment. They stressed that hearing loss in these patients may be due to aging than to hypothyroidism. [93]

Several studies were done to find the normative data of BAER parameters have found that no significant difference was exist between the right and left ears. [14] Similar to the above studies there is no statistically significant inter aural difference found in this study (Table-6). But De lorenzeo et al measured inter auricular difference of 0.2ms of wave latencies. [78]

In the present study there was positive correlation of BAER latencies with serum TSH and negative correlation with serum free thyroid hormone levels. This was consistent with the following study results. Himelfarb et al found statistically significant relation between the hearing loss and the serum level of low free T4. [80]

Ben Tovim et al done an experimental study on rats, inferred that the BAER changes are directly associated with the serum level of free T4. This correlation suggests that there is direct involvement

of auditory pathway by thyroid hormone deficiency and results in delaying of impulse transmission time in BAER recordings.[82]

Many studies have shown that treatment of hypothyroidism with thyroid hormone reverse the SNHL. A prospective study done in goitrous hypothyroidism patients found both subjective and objective improvement in hearing after thyroxine treatment.[15] Karlos et al[11], Yumnam et al[16], Thorton et al[73] also showed the improvement in the BAER latencies after thyroxine supplementation. They reasoned out that, thyroid hormone enhances the synthesis and release of neurotransmitters and also increases the receptor sensitivity. So early identification of the involvement of nervous system and auditory pathway using brainstem auditory evoked response will help us to prevent the occurrence of sensori neural hearing loss in hypothyroid patients.

SUMMARY

SUMMARY

- Brainstem auditory evoked responses were recorded in newly diagnosed hypothyroid females and normal healthy females.
- The BAER parameters namely absolute and inter peak latencies were analyzed between two groups.
- There was significant prolongation of absolute latencies of waves I, III and V observed in newly diagnosed hypothyroid females.
- The inter peak latencies I- III, III - V and I -V were also increased significantly in newly diagnosed hypothyroid females compared to normal healthy females.
- There was direct correlation between thyroid profile and BAER latencies.
- There was no significant difference of BAER latencies between right and left ear in newly diagnosed hypothyroid females.

CONCLUSION

CONCLUSION

Hearing enables us to collect, process and interpret sounds continuously and without conscious effort. Once sense of hearing is fully lost there is no substitute. None of the other senses could replace the phenomenon of hearing sound; that is why hearing is our most valuable sense. Life is better when we hear better!

When hearing is lost, it will lead to confusion, embarrassment, anxiety, depression, frustration, social isolation and diminished work capacity. Though impairment of hearing at an early stage appears negligible, it should not be neglected.

In hypothyroidism hearing loss is the most common otolaryngological manifestation . Hypothyroidism is a multiorgan endocrine disorder which affects the auditory pathway in a diffuse pattern and causes retro cochlear sensori neural hearing loss(SNHL). About 25% of adult hypothyroid patients have significant hearing loss. This is because, thyroid hormone deficiency causes delayed neuronal impulse transmission along the auditory pathway as it plays a vital role in the development, maturation and myelination of auditory pathway.

Unlike other causes of SNHL, hypothyroidism induced hearing loss will be completely curable with thyroxine substitution. So early diagnosis of auditory pathway involvement in hypothyroidism will help us to initiate early treatment. With advancement of computer signal processing the early diagnosis can be done by evoked potential studies. Among those studies BAER is a highly sensitive, specific, noninvasive and reproducible method for detecting the early alterations in the brainstem auditory pathway. It not only gives the information about the auditory pathway, but also tells about the central nervous system involvement.

In the present study, we found a significant prolongation of absolute latencies and inter peak latencies of brainstem auditory evoked responses in newly diagnosed hypothyroid individuals even before the hearing loss overt. So it should be recommended that BAER may be added to the list of screening tools for a more accurate and early assessment of neurological involvement in hypothyroid individuals to initiate treatment to ameliorate symptoms and prevent complications. Because Better hearing gives better life promise.

FUTURE STUDY PLAN:

The current study is of public health importance as it suggests that the recording of BAER in newly diagnosed hypothyroid patients and thereby advice patients regarding early treatment and prevention of complications.

- This study can be further extended in these patients after attaining euthyroid state to find out the reversibility of SNHL.
- This study can be done among children suffering from hypothyroidism to determine the role of thyroxine on the development of hearing.

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ANNEXURES

CONSENT FORM

Dr. V. Roseline Jesintha, Post graduate student in the Department of Physiology, Coimbatore Medical College is studying the "BRAINSTEM AUDITORY EVOKED RESPONSES IN NEWLY DIAGNOSED HYPOTHYROID INDIVIDUALS". The procedure of estimation of free T_3, free T_4 and TSH and recording of Brainstem Auditory Evoked Responses were explained to me clearly.

I hereby give my consent to participate in this study. The data obtained herein may be used for research and publication.

Name :

Place :

Signature :

PROFORMA

Name:

Age:

Sex:

Occupation:

Address: Ph. No:

Present illness:

H/o hoarseness of voice
H/o cold intolerance
H/o cramps
H/o numbness
H/o constipation/diarrhea
H/o loss of hair
H/o tinnitus
H/o hard of hearing
H/o vertigo
H/o fever

Menstrual H/o:

H/o menorrhagia
Duration : No. of pads / day:
H/o passing of clots
H/o associated abdominal pain

Past H/O:

H/o drug intake
H/o thyroid surgery
H/o previous hospital admission
H/o radiation exposure

Family H/O:

H/o thyroid disorder
H/o hearing disorder
Chronic illness: SHT, DM, IHD, TB, BA, EPILEPSY

GENERAL EXAMINATION

Built:

Height:

Weight: BMI:

VITALS:

PR: RR:

BP: Temp:

SYSTEM EXAMINATION:

CVS:

RS:

Abdomen:

CENTRAL NERVOUS SYSTEM

1. Examination of the Motor System
2. Examination of the Sensory System
3. Examination of Reflexes

INVESTIGATIONS

Thyroid profile:

Serum fT3

Serum f T4

TSH

Otoscopy Features:

External Auditory Canal

Tympanic Membrane

Hearing Tests:

Rinne's Test

Weber's Test

Brainstem Auditory Evoked Response:

Waves	Right Ear	Left Ear
Absolute Latencies		
I		
III		
V		
Inter Peak Latencies		
I – III		
III - V		
I - V		

MASTER CHART

Master Chart 1: Newly diagnosed Hypothyroid Females

S.No	Age	Height	Weight	BMI	Serum TSH (mIU/ml)	Serum f T3 (pg/ml)	Serum f T4 (ng/ml)	Right Ear						Left Ear					
								I	III	V	I-III	III-V	I-V	I	III	V	I-III	III-V	I-V
1	45	155	68	28.3	18.92	1.98	0.88	2.42	5.5	8.65	3.1	2.5	5.6	2.47	5.64	8.68	3.14	2.63	5.72
2	33	158	64	25.64	39.92	1.5	0.69	2.8	6.3	8.84	3.53	3.1	6.5	2.72	6.1	8.6	3.48	2.96	6.46
3	46	150	66	29.3	10.5	1.23	0.58	2.17	5.08	7.7	2.91	2.62	5.53	2.12	4.1	6.88	2.98	2.78	5.76
4	48	149	58	26.12	9.8	2.12	1.24	1.6	4.2	7.38	2.62	2.3	5.93	1.8	4.18	7.45	2.38	2.25	5.63
5	39	155	59	24.56	19.93	1.21	0.72	1.98	3.55	6.03	1.57	1.48	6.05	1.9	3.45	6.38	2.35	1.93	6.28
6	28	160	68	26.56	124.5	0.24	0.12	2.78	6.3	8.93	3.46	2.9	6.52	2.72	6.4	8.73	3.64	2.9	6.58
7	35	148	56	25.57	11.8	0.65	0.46	2.5	5.6	8.63	3.14	2.56	6.61	2.42	5.53	8.65	3.12	2.48	6.54
8	23	160	60	23.44	8.7	1.68	1.12	1.88	4.6	8.03	2.8	3.4	5.15	1.5	4.8	8.1	3.03	3.32	5.35
9	46	155	64	26.6	59.6	1.4	0.74	1.65	4.4	8.5	3.03	2.81	5.8	1.8	4.35	8.68	2.55	2.8	5.35
10	28	158	60	24.03	9.38	1.46	0.78	1.76	4.6	7.94	3.14	2.47	6.03	1.88	4.97	8.03	3.24	2.68	6.12
11	44	152	56	24.24	50.48	0.8	0.52	1.82	4.28	6.16	2.56	1.87	4.43	1.92	4.22	6.18	2.3	1.96	4.26
12	36	151	50	21.93	17.2	0.5	0.38	2.22	4.4	7.84	2.94	2.67	5.73	2.24	4.94	7.76	2.88	2.72	5.72
13	44	153	54	23.07	9.52	1.24	0.72	2.18	4.7	8.28	2.94	2.56	6.1	2.15	4.75	8.3	3.1	2.64	6.21
14	40	157	60	24.34	11.1	0.58	0.48	1.68	3.45	6.3	2.27	1.85	4.62	1.65	2.68	6.45	1.65	1.56	4.58
15	38	155	60	24.9	26.4	2.4	1.4	1.64	4.1	7.73	2.5	2.2	4.7	1.76	4.88	7.86	2.67	2.64	4.9
16	29	148	55	25.1	92.6	0.68	0.41	2.7	6.3	8.93	3.4	2.9	6.4	2.72	6.4	8.7	3.7	3.1	6.5
17	32	153	53	22.6	23.5	0.59	0.39	2.56	5.7	8.4	2.7	2.3	5.4	2.14	5.6	8.1	2.7	2.5	5.6
18	31	156	60	24.6	9.9	1.2	0.69	1.64	4.2	7.38	2.62	2.3	4.93	1.8	4.18	7.45	2.38	2.25	4.6
19	41	154	57	24.03	40.6	0.92	0.51	1.88	4.5	8.04	2.9	3.5	6.16	1.5	4.8	8.13	3.04	3.33	6.35
20	28	156	66	27.12	152.8	0.9	0.49	1.92	4.5	7.88	2.84	2.43	5.96	2.04	4.63	7.94	3.04	2.56	6.12
21	35	154	60	25.3	52.1	0.79	0.4	2.56	5.7	8.4	2.7	2.3	5.46	2.14	5.6	8.1	2.7	2.5	5.6
22	36	152	60	25.97	31.5	0.81	0.44	2.5	5.5	8.78	3.45	2.5	5.67	2.6	5.7	8.8	3.4	2.5	5.58
23	29	150	54	24	39.83	1.2	0.74	1.45	5.1	7.05	3.5	2.95	5.6	1.5	4.8	7.36	2.83	2.5	5.56
24	34	148	55	25.11	28.89	1.74	0.8	1.5	4.2	4.23	2.64	2.4	5.02	1.6	4.23	7.5	2.6	2.4	4.98
25	41	146	54	25.33	39.82	1.32	0.65	1.76	4.6	7.94	3.14	2.27	6.03	1.88	4.97	8.03	3.24	2.68	6.12
26	28	157	67	27.18	90.9	0.96	0.51	2.18	4.7	8.28	2.94	2.56	6.1	2.15	4.75	8.3	3.1	2.64	6.21
27	37	148	52	23.74	12.8	0.98	0.34	1.92	4.5	7.8	2.84	2.34	5.96	2.04	4.63	7.94	3.04	2.56	6.1
28	38	154	60	25.3	38.1	0.45	0.28	2.4	5.5	8.56	3.2	2.56	6.04	2.45	5.38	8.36	3.16	2.48	6.02
29	45	152	58	25.1	15.2	0.59	0.3	1.85	4.3	6.98	2.45	2.68	5.13	1.8	3.26	6.28	2.35	2.6	5.01
30	42	160	65	25.39	28.9	1.32	0.81	1.6	4.6	7.8	3.4	3.1	5.9	1.6	4.6	8.7	2.45	2.46	5.2
31	40	153	68	29.05	80.6	0.35	0.28	2.48	5.7	8.65	3.4	2.5	5.4	2.54	5.64	8.79	3.12	2.45	5.7
32	42	148	56	25.57	12.6	0.64	0.4	1.76	4.6	8.21	3.16	2.68	6.14	1.78	4.68	8.24	3.04	2.84	6.12
33	39	170	68	23.53	29.86	1.8	0.71	1.69	4.2	7.6	2.4	2.56	5.68	1.78	4.4	7.8	2.7	2.6	5.9
34	48	153	57	24.35	18.64	2.4	0.98	1.66	4.6	7.2	2.88	2.56	5.88	2.1	4.56	7.5	3.2	3.1	6.4
35	33	152	54	23.37	30.8	0.85	0.55	1.88	4.7	7.88	2.88	2.76	5.88	1.94	4.56	7.94	2.86	2.74	5.92
36	41	145	55	26.16	110.7	0.34	0.19	2.78	6.3	8.93	3.46	2.9	6.52	2.72	6.4	8.73	3.64	2.9	6.58
37	42	148	55	25.11	17.9	0.52	0.2	2.56	5.7	8.4	2.7	2.3	5.4	2.14	5.6	8.1	2.7	2.5	5.6
38	26	160	64	25	29.65	1.14	0.6	1.82	4.3	8.9	3.5	2.86	6.45	1.8	4.71	8.24	3.1	2.9	6.22
39	22	162	72	27.43	75.4	0.72	0.48	1.8	4.3	8.9	3.5	2.86	6.5	1.8	4.71	8.24	2.9	2.9	6.12
40	50	152	60	25.97	100.6	1.5	0.48	1.74	4.5	7.19	2.5	2.6	6.5	1.7	4.5	8.9	2.6	2.9	6.4

BMI - Body Mass Index
f T3 - free Triiodotyrosine
f T4 - free Tetraiodotyrosine
TSH - Thyroid Stimulating Hormone

Master Chart 2: Healthy Females

S.No	AGE	HEIGHT	WEIGHT	BMI	Serum TSH (mIU/L)	Serum f T3 (pg/ml)	Serum f T4 (ng/dl)	RIGHT EAR						LEFT EAR					
								I	III	V	I-III	III-V	I-V	I	III	V	I-III	III-V	I-V
1	25	165	60	22.04	2.1	2.4	1.1	1.84	4.35	6.42	2.51	2.07	4.58	1.82	4.35	6.38	2.53	2.03	4.56
2	45	170	67	23.18	2.24	3.21	1.02	2.56	5.7	8.4	2.7	2.3	5.4	2.14	5.6	8.1	2.7	2.5	5.6
3	24	155	58	24.14	3.47	3.83	1.3	1.23	3.58	6.18	2.35	2.23	4.95	1.27	3.42	6.18	2.76	2.16	4.91
4	50	153	55	23.5	0.58	5.02	0.91	1.05	3.32	5.75	2.43	2.27	4.7	1.1	2.68	4.65	1.97	1.6	4.57
5	48	148	55	25.11	3.5	2.65	1.42	1.5	3.58	6.02	2.3	2.44	4.47	1.18	2.7	4.3	1.68	1.56	4.22
6	35	160	68	26.56	2.81	2.54	0.8	1.25	2.6	4.15	1.55	1.45	3.12	1.23	2.65	4.45	1.52	1.39	3.35
7	44	153	60	25.63	2.45	2.3	1.04	1.45	4.5	6.2	2.46	2.34	4.2	1.5	4.42	7.16	2.26	2.14	4
8	28	156	55	22.6	4.5	2.35	1.06	1.5	4.8	5.9	3.2	2.8	5.2	1.6	4.42	6.16	3.06	2.84	5.06
9	36	160	60	23.44	3.7	3.8	1.5	1.24	3.48	4.52	1.83	1.14	3.97	1.12	3.08	4.9	1.96	1.23	3.89
10	40	154	62	26.14	3.24	3.56	0.93	1.58	3.45	5.68	2.6	2.23	3.84	1.78	3.48	6.32	2.7	2.14	4.54
11	23	152	52	22.51	2.42	3.81	0.95	1.38	3.28	5.26	1.68	1.8	3.48	1.28	3.28	5.52	2.18	1.92	3.54
12	34	150	56	24.89	3.3	2.6	1.21	1.1	2.98	4.8	1.88	1.78	4.3	1.05	3.32	5.55	2.27	2.13	4.5
13	26	160	62	24.22	3.72	3.34	1.08	1.23	2.65	4.58	2.42	1.93	3.35	1.13	2.6	4.15	2.45	2.15	4.15
14	49	162	60	22.86	4.5	4.12	1.6	1.02	3.4	4.68	2.28	2.08	3.66	1.02	3.06	4.64	2.8	2.33	4.18
15	28	155	54	22.48	2.02	4.6	1.41	1.12	2.68	4.45	1.68	1.77	3.53	1.08	2.45	4.53	1.85	1.77	3.62
16	32	153	49	20.93	1.44	2.31	0.93	1.6	4.6	7.8	3.4	3.1	5.5	1.6	4.6	6.7	2.45	2.36	4.25
17	30	150	54	24	1.22	2.72	0.78	1.27	3.52	5.92	2.25	2.4	4.56	1.38	4.25	6.24	2.53	2.07	4.6
18	43	148	49	22.37	3.24	3.46	0.69	1.58	3.4	6.89	2.45	2.38	4.32	1.48	4.28	6.28	2.54	1.69	4.38
19	29	152	56	24.24	2.1	2.58	0.58	1.8	3.4	5.35	1.96	1.59	4.55	1.8	3.42	5.44	2.26	1.9	4.62
20	36	158	60	24.03	0.98	3.12	1.04	1.18	2.85	5.05	1.67	2.2	3.7	1.2	3.42	5.02	1.58	1.4	3.72
21	45	154	56	23.61	4.52	3.02	1.09	1.9	3.5	5.3	1.78	1.69	3.46	1.85	2.89	4.54	1.82	1.6	3.64
22	35	160	65	25.39	3.12	2.81	1.23	1.82	4.9	6.58	2.62	2.4	5	1.8	4.23	7.5	2.6	2.4	4.89
23	25	162	58	22.1	0.74	3.58	1.2	1.28	4.3	5.8	2.45	2.15	3.91	1.32	3.45	5.1	1.63	1.53	4.18
24	26	154	61	25.72	2.56	2.62	1.05	1.12	4.1	4.88	2.5	1.78	4.16	1.27	3.52	5.02	1.52	1.4	4.35
25	46	158	49	19.63	0.94	2.81	1.4	1.7	3.6	5.6	2.2	2.1	4.2	1.7	3.6	5.5	2.2	2.1	4.1
26	37	146	50	23.46	1.82	3.1	0.89	1.63	4.28	6.5	2.65	2.22	4.88	2.17	4.33	6.65	2.15	2.28	4.38
27	48	152	55	23.81	1.96	4.5	1.34	1.49	3.57	5.4	2.08	1.87	3.94	1.49	3.5	5.35	2.01	1.85	3.86
28	24	158	58	23.23	4.48	2.9	1.2	1.5	4.1	5.6	2.12	2.01	5.2	1.8	4.5	5.1	2.2	2.13	5.2
29	28	156	53	21.78	3.2	3.62	0.59	1.58	3.67	5.57	2.08	1.91	3.99	1.55	3.75	5.75	2.17	1.82	3.94
30	39	150	48	21.33	2.48	4.02	0.78	1.08	3.88	5.69	2.5	2.12	3.97	0.95	4.2	5.43	2.25	2.13	3.48
31	42	164	55	20.45	0.94	4.1	1.42	2.22	3.4	6.84	2.94	2.67	4.73	2.24	4.49	6.76	2.88	2.72	4.72
32	46	156	54	22.19	1.54	3.72	0.88	1.72	4.28	6.15	2.56	1.87	4.43	1.92	4.22	6.18	2.3	1.96	4.26
33	32	150	50	22.22	2.1	2.81	1.4	1.54	4.1	5.23	2.45	2.3	4.61	2.42	4.53	6.65	2.21	2.1	4.81
34	36	148	51	23.28	4.34	3.9	0.96	1.63	4.28	6.5	2.65	2.22	4.88	2.17	4.33	6.64	2.15	2.28	4.38
35	32	152	48	20.78	0.91	3	0.8	0.98	2.5	4.62	1.58	1.12	3.64	0.92	3.3	4.8	1.64	1.25	3.68
36	26	154	50	21.08	4.2	3.5	1.45	2.3	4.9	5.5	2.52	2.4	4.98	1.9	4.23	6.5	2.5	2.4	4.89
37	45	156	49	20.13	0.58	4.01	0.94	1.5	4.26	5.56	2.1	1.9	5.1	1.7	3.98	5.15	1.98	1.84	4.92
38	49	152	50	21.64	1.24	2.69	1.57	1.35	3.9	4.91	1.89	1.76	4.9	1.5	3.69	4.86	1.58	1.4	4.7
39	39	158	52	20.83	3.8	3.2	0.82	1.45	3.05	4.75	1.6	1.53	3.31	1.35	2.69	4.28	1.75	1.53	3.1
40	36	154	62	26.14	0.45	4.2	1.62	2.3	4.53	6.08	2.5	2.2	4.7	1.76	4.88	6.06	2.67	2.64	4.9

BMI - Body Mass Index
f T3 - free Triiodotyrosine
f T4 - free Tetraiodotyrosine
TSH - Thyroid Stimulating Hormone